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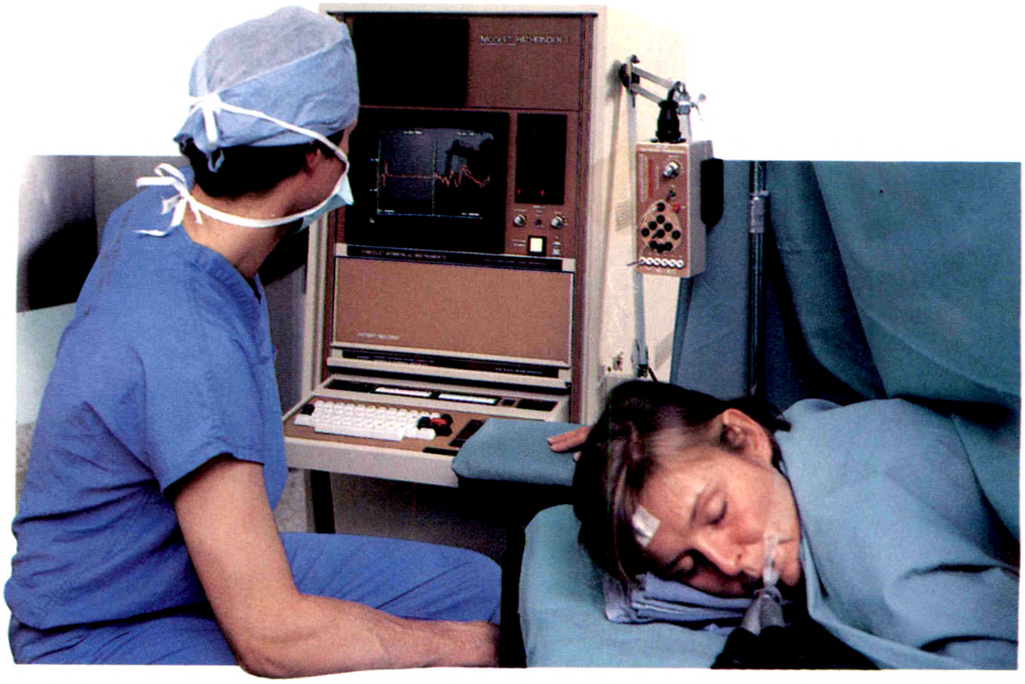

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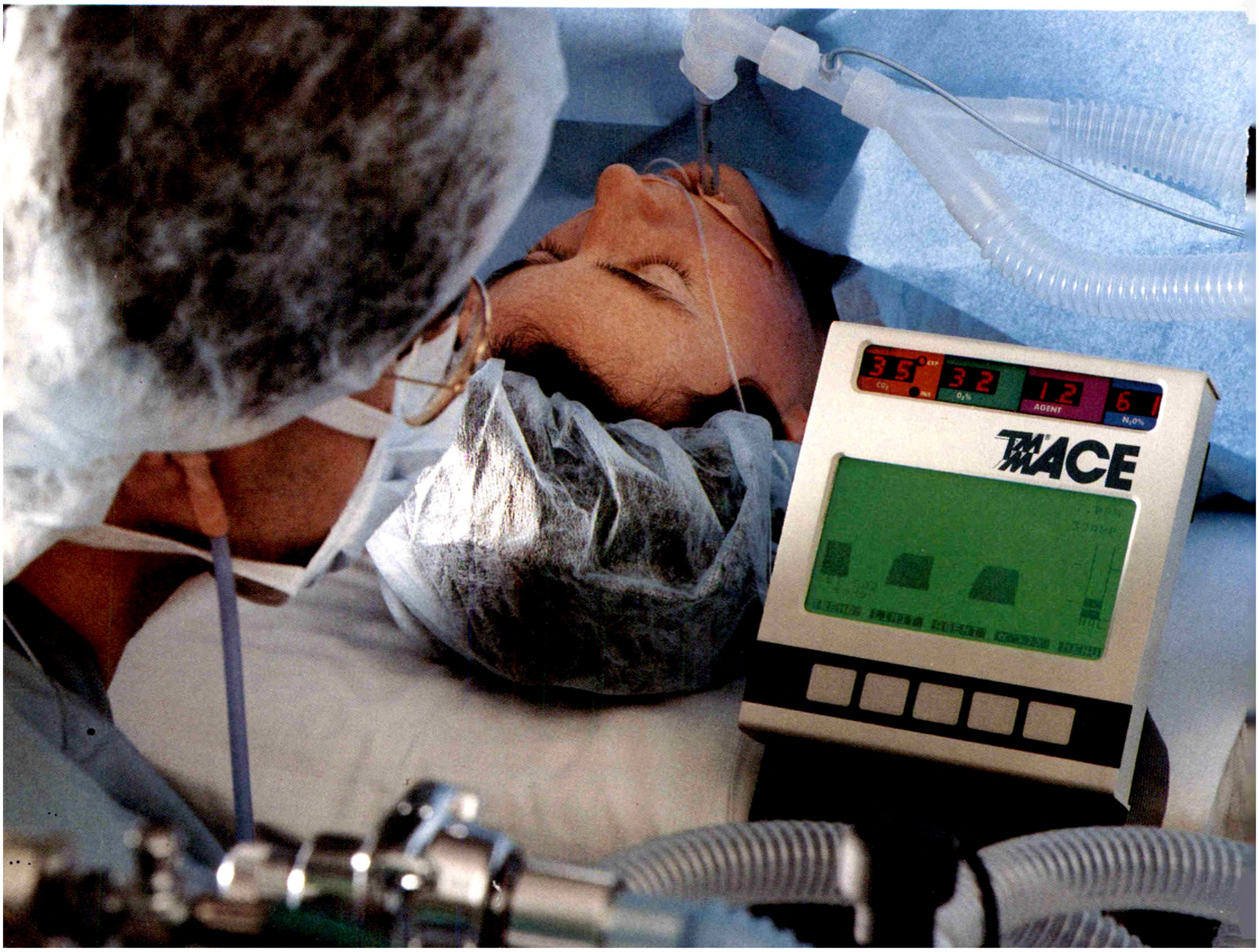

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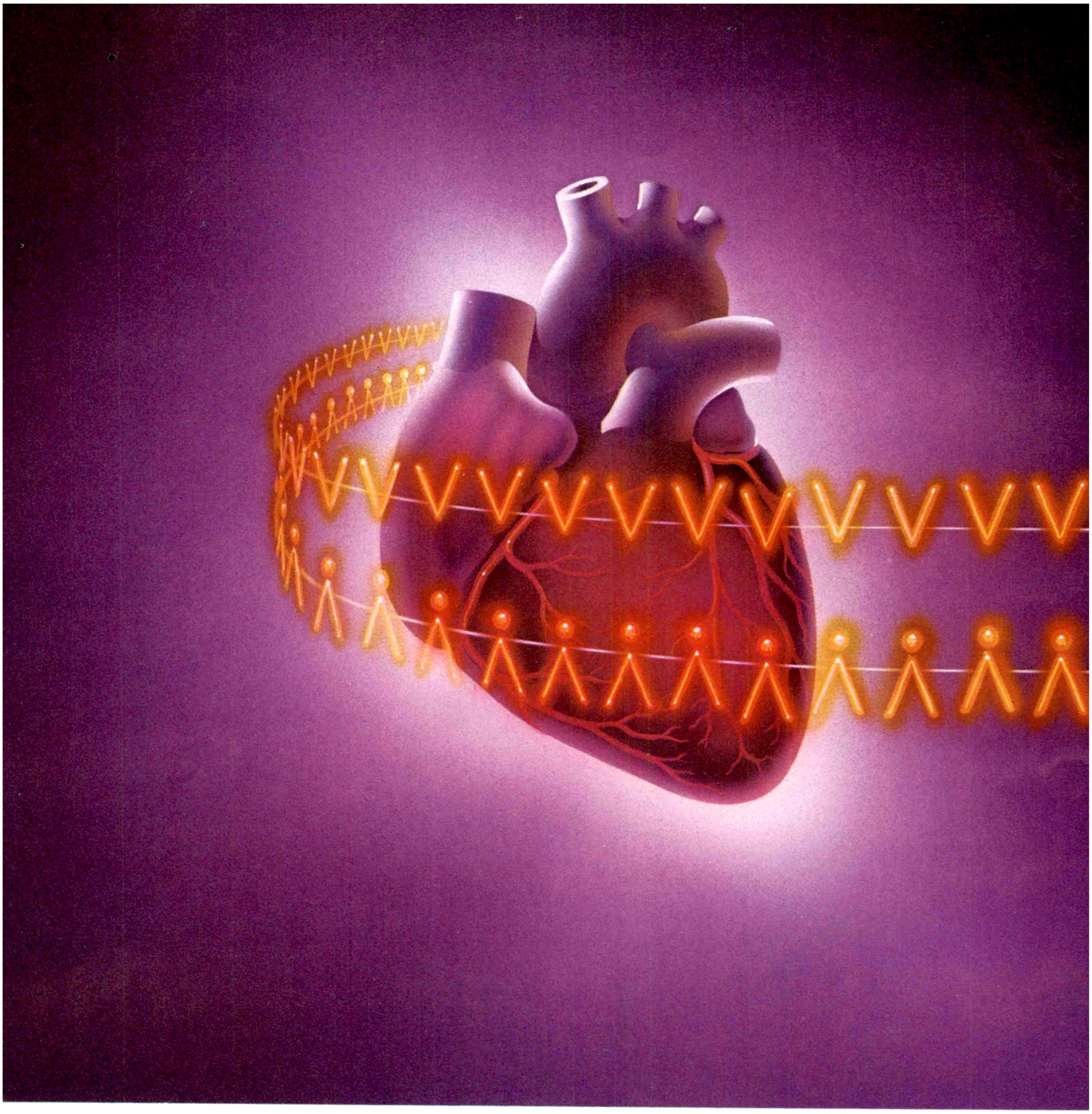

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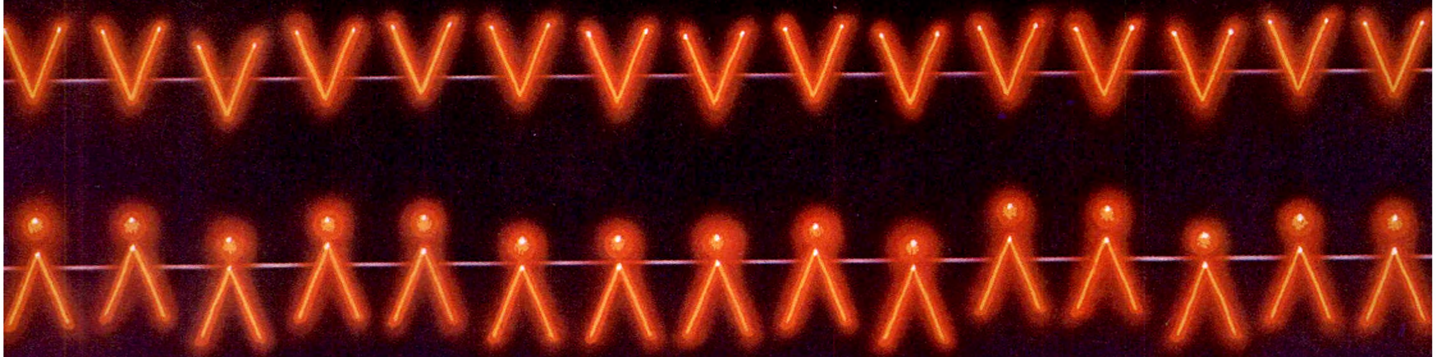

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Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were:

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OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

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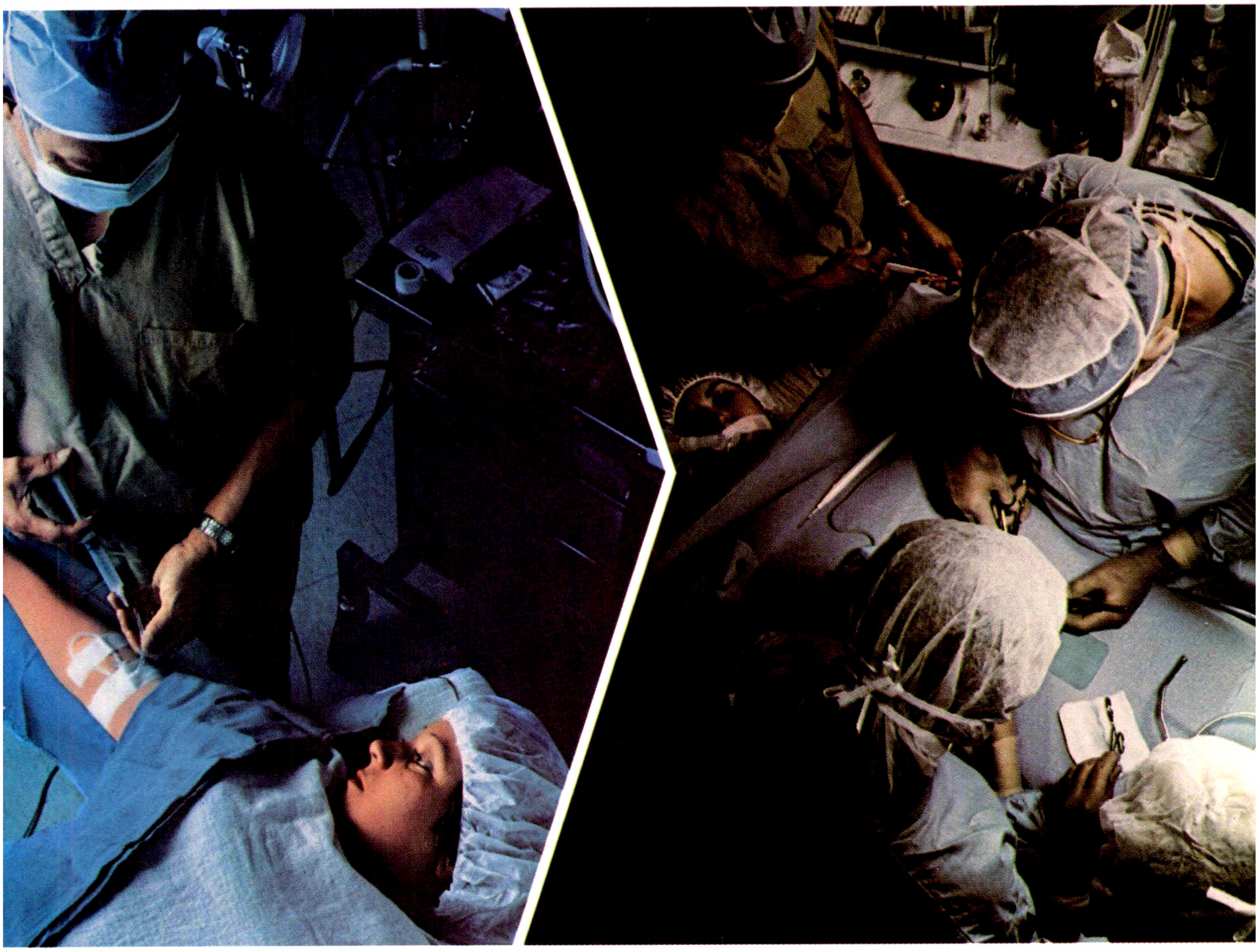

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brand of midazolam HCl Roche (IV)

equivalent to 1 mg/mL and 5 mg/mL

Please see references and summary of product information on the following page

References: 1. Data on file (Doc. #069-001, 004, 005, 007), Roche Laboratories. **2.** VERSED® (brand of midazolam HCl/Roche) ©, Scientific Summary, Roche Laboratories, Division of Hoffmann-La Roche Inc., Nutley, NJ. 1986.

VERSED®
(brand of midazolam HCl/Roche) ©
INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS: IM: preoperative sedation; to impair memory of perioperative events. **IV:** conscious sedation prior to short diagnostic or endoscopic procedures, alone or with a narcotic; induction of general anesthesia before administration of other anesthetic agents; as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia) for short surgical procedures (longer procedures have not been studied). When used IV, VERSED is associated with a high incidence of partial or complete impairment of recall for the next several hours.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma, may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen and resuscitative equipment for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression; should be administered as induction agent only by a person trained in general anesthesia. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred, predominantly in older chronically ill patients and/or with concomitant use of other cardiorespiratory depressant agents. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs.

Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Higher risk surgical or debilitated patients require lower dosages for induction of anesthesia, premedicated or not.

Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure have a 1.5- to 2-fold increase in elimination half-life, total body clearance and volume of distribution of midazolam. Patients with congestive heart failure have a 2- to 3-fold increase in the elimination half-life and volume of distribution of midazolam. Patients over 55 require lower dosages for induction of anesthesia, premedicated or not. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: *General:* Increased cough reflex and laryngospasm may occur with peroral endoscopic procedures. Use topical anesthetic and make necessary countermeasures available; use narcotic premedication for bronchoscopy. Decrease intravenous doses by about 30% for elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or circulatory effects noted following administration of succinylcholine.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant. 3. Inform your physician if you are nursing.

Drug interactions: The hypnotic effect of intravenous VERSED is accentuated by premedication, particularly narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage of VERSED according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of intramuscular VERSED for premedication.

The use of VERSED as an induction agent may result in a reduction of the inhalation anesthetic requirement during maintenance of anesthesia.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: The use of injectable VERSED in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness of VERSED in children below the age of 18 have not been established.

ADVERSE REACTIONS: Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. Serious cardiorespiratory adverse events have also occurred. (See WARNINGS.)

In the conscious sedation studies, hypotension occurred more frequently after IV administration in patients concurrently premedicated with meperidine. During clinical investigations, three cases (0.2%) of transient fall in blood pressure greater than 50% were reported during the induction phase.

Reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity and combativeness have been reported. (See DOSAGE AND ADMINISTRATION.)

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special Sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. *Miscellaneous:* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

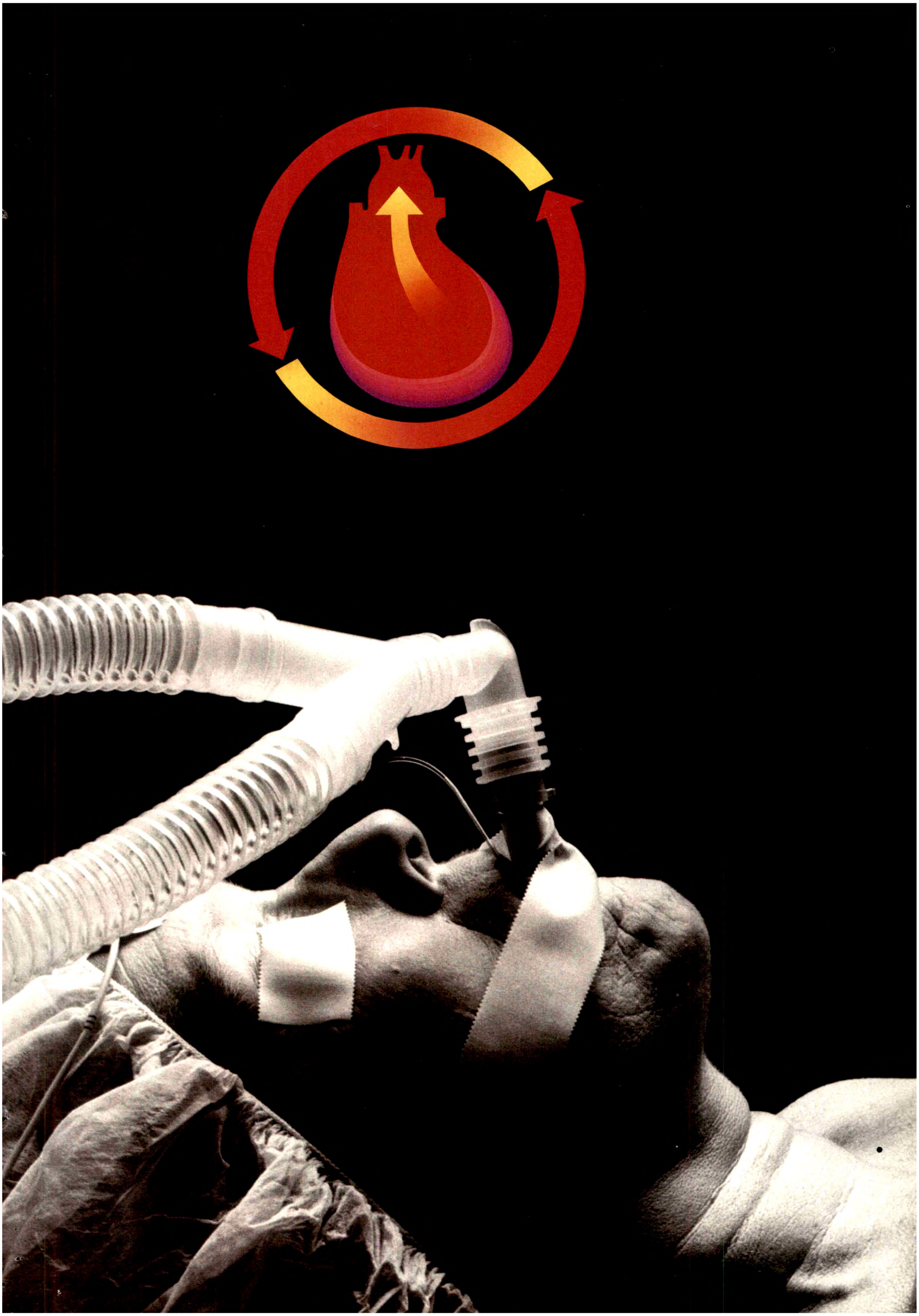
Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

DOSAGE AND ADMINISTRATION: Individualize dosage. Elderly and debilitated patients generally require lower doses. Adjust dose of IV VERSED according to type and amount of premedication. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest, especially in elderly or debilitated patients. (See WARNINGS.) *IM use:* Inject deep in large muscle mass. *IV use:* Administer initial dose over 20 to 30 seconds for induction of general anesthesia. For conscious sedation administer initial dose over 2 to 3 minutes. May be mixed in the same syringe with morphine sulfate, meperidine, atropine sulfate or scopolamine. Compatible with 5% dextrose in water, 0.9% sodium chloride and lactated Ringer's solution.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (*e.g.*, sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

ROCHE®
ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

P.I. 0387



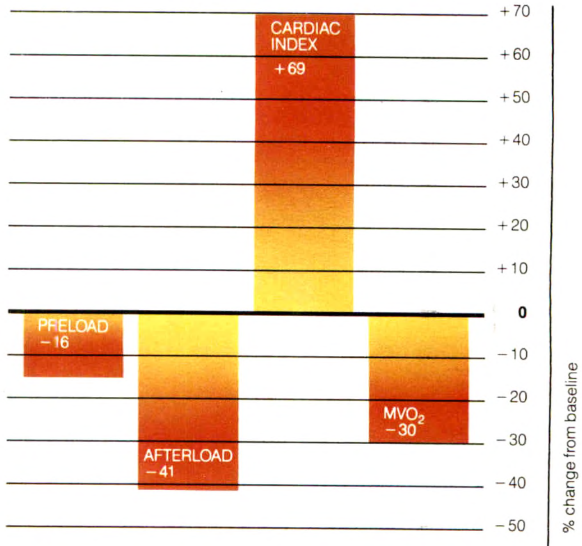
Dual action INOCOR® I.V. (AMRINONE) Inotropic plus vasodilating action in a single drug.

Two-in-one action can improve hemodynamic response after cardiac surgery.

In patients with congestive heart failure due to coronary artery disease, INOCOR I.V. increases CI and decreases preload and afterload without increasing MVO_2 or significantly increasing risk of arrhythmias.

*INOCOR I.V. is "...an extremely useful tool....I have been using amrinone...[for] inotropic support to wean patients from cardiopulmonary bypass and as a means of increasing [CI] in the post-bypass period."**

Roberta Hines, M.D.
Yale University School of Medicine
Yale University Hospital



†n = 8. Amrinone was infused at 2.5 mg/kg over 1 hour. Adapted from Benotti et al.[1]

Please see last page for important product information concerning contraindications, adverse reactions, patient selection, and precautionary recommendations.

*Interview on file, Winthrop Pharmaceuticals.

State-of-the-heart

Inocor® I.V.

(AMRINONE)

Dual-acting therapy, instead of catecholamines


State-of-the-heart
therapy.
(Brief Summary—see next page)

INOCOR I.V.

Two-in-one dual inotropic and vasodilator action provides improved therapy for the cardiac surgery patient.

- Unlike catecholamines, INOCOR does not increase MVO_2 and can be used in ischemic patients with heart failure.
- Unlike catecholamines, INOCOR does not act on the beta receptors—may be effectively used in patients on beta blockers.
- Unlike catecholamines, INOCOR does not significantly increase risk of arrhythmias (see Precautions).
- INOCOR has not been shown to interact with anesthetic agents.

Please consult full product information before prescribing. A summary follows.

INOCOR lactate injection, brand of amrinone lactate, represents a new class of cardiac inotropic agents with vasodilator activity, distinct from digitalis glycosides or catecholamines.

INDICATIONS AND USAGE (INOCOR lactate injection is indicated for the short-term management of congestive heart failure in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators.)

INOCOR lactate injection is indicated for the short-term management of congestive heart failure. Because of limited experience and potential for serious adverse effects (see ADVERSE REACTIONS), INOCOR should be used only in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators. Although most patients have been studied hemodynamically for periods only up to 24 hours, some patients were studied for longer periods and demonstrated consistent hemodynamic and clinical effects. The duration of therapy should depend on patient responsiveness.

CONTRAINDICATIONS INOCOR lactate injection is contraindicated in patients who are hypersensitive to it.

It is also contraindicated in those patients known to be hypersensitive to bisulfites.

PRECAUTIONS *General:* INOCOR lactate injection should not be used in patients with severe aortic or pulmonic valvular disease in lieu of surgical relief of the obstruction. Like other inotropic agents, it may aggravate outflow tract obstruction in hypertrophic subaortic stenosis.

During intravenous therapy with INOCOR lactate injection, blood pressure and heart rate should be monitored and the rate of infusion slowed or stopped in patients showing excessive decreases in blood pressure.

Patients who have received vigorous diuretic therapy may have insufficient cardiac filling pressure to respond adequately to INOCOR lactate injection, in which case cautious liberalization of fluid and electrolyte intake may be indicated.

Supraventricular and ventricular arrhythmias have been observed in the very high-risk population treated. While amrinone per se has not been shown to be arrhythmogenic, the potential for arrhythmia, present in congestive heart failure itself, may be increased by any drug or combination of drugs.

Thrombocytopenia and hepatotoxicity have been noted (see ADVERSE REACTIONS).

LABORATORY TESTS *Fluid and electrolytes:* Fluid and electrolyte changes and renal function should be carefully monitored during amrinone lactate therapy. Improvement in cardiac output with resultant diuresis may necessitate a reduction in the dose of diuretic. Potassium loss due to excessive diuresis may predispose digitalized patients to arrhythmias. Therefore, hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use.

DRUG INTERACTIONS In a relatively limited experience, no untoward clinical manifestations have been observed in patients in whom INOCOR lactate injection was used concurrently with the following drugs: digitalis glycosides, lidocaine, quinidine, metoprolol, propranolol; hydralazine, prazosin, isosorbide dinitrate, nitroglycerine; chlorthalidone, ethacrynic acid, furosemide, hydrochlorothiazide, spironolactone, captopril, heparin, warfarin, potassium supplements, insulin, diazepam.

One case of excessive hypotension was reported when amrinone was used concurrently with disopyramide.

Until additional experience is available, concurrent administration with Norpace® disopyramide should be undertaken with caution.

USE IN ACUTE MYOCARDIAL INFARCTION INOCOR is not recommended for use in acute myocardial infarction.

USE IN CHILDREN Safety and effectiveness in children have not been established.

USE IN PREGNANCY *Pregnancy category C.* In New Zealand white rabbits, amrinone has been shown to produce fetal skeletal and gross external malformations at oral doses of 16 mg/kg and 50 mg/kg that were toxic for the rabbit. Studies in French Hy/Cr rabbits using oral doses up to 32 mg/kg/day did not confirm this finding. No malformations were seen in rats receiving amrinone intravenously at the maximum dose used, 15 mg/kg/day (approximately the recommended daily IV dose for patients with congestive heart failure). There are no adequate and well-controlled studies in pregnant women. Amrinone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

USE IN NURSING MOTHERS Caution should be exercised when amrinone is administered to nursing women, since it is not known whether it is excreted in human milk.

ADVERSE REACTIONS *Thrombocytopenia:* Intravenous INOCOR lactate injection resulted in platelet count reductions to below 100,000/mm^3 in 2.4% of patients.

Gastrointestinal effects: Gastrointestinal adverse reactions reported with INOCOR lactate injection during clinical use included nausea (1.7%), vomiting (0.9%), abdominal pain (0.4%), and anorexia (0.4%).

Cardiovascular effects: Cardiovascular adverse reactions reported with INOCOR lactate injection include arrhythmia (3%) and hypotension (1.3%).

Hepatic toxicity: In dogs, at IV doses between 9 mg/kg/day and 32 mg/kg/day, amrinone showed dose-related hepatotoxicity manifested either as enzyme elevation or hepatic cell necrosis or both. Hepatotoxicity has been observed in man following long-term oral dosing and has been observed, in a limited experience (0.2%), following IV administration of amrinone.

Hypersensitivity: There have been reports of several apparent hypersensitivity reactions in patients treated with oral amrinone for about two weeks. Signs and symptoms were variable but included pericarditis, pleuritis, and ascites (one case); myositis with interstitial shadowing on chest x-ray and elevated sedimentation rate (one case); and vasculitis with nodular pulmonary densities, hypoxemia, and jaundice (one case). The first patient died, not necessarily of the possible reaction, while the last two resolved with discontinuation of therapy. None of the cases were rechallenged, so attribution to amrinone is certain, but possible hypersensitivity reactions should be considered in patient maintained for a prolonged period on amrinone.

General: Additional adverse reactions observed in intravenous amrin clinical studies include fever (0.9%), chest pain (0.2%), and burning at the sit injection (0.2%).

OVERDOSAGE Doses of INOCOR lactate injection may produce hypotens because of its vasodilator effect. If this occurs, amrinone administration sho be reduced or discontinued. No specific antidote is known, but gen measures for circulatory support should be taken.

MANAGEMENT OF ADVERSE REACTIONS *Platelet count reductic* Asymptomatic platelet count reduction (to less than 150,000/mm^3) may reversed within one week of a decrease in drug dosage. Further, with no cha in drug dosage, the count may stabilize at lower than predrug levels without clinical sequelae. Predrug platelet counts and frequent platelet counts dur therapy are recommended to assist in decisions regarding dos modifications.

Should a platelet count less than 150,000/mm^3 occur, the follow actions may be considered:

- Maintain total daily dose unchanged, since in some cases counts have eit stabilized or returned to pretreatment levels.
- Decrease total daily dose.
- Discontinue amrinone if, in the clinical judgment of the physician, risk exce the potential benefit.

Gastrointestinal side effects: While gastrointestinal side effects were s infrequently with IV therapy, should severe or debilitating ones occur, physician may wish to reduce dosage or discontinue the drug based on usual benefit-to-risk considerations.

Hepatic toxicity: In clinical experience to date with IV administration, hep toxicity has rarely been observed. If acute marked alterations in liver enzyn occur together with clinical symptoms, suggesting an idiosyncratic hyperse tivity reaction, amrinone therapy should be promptly discontinued.

If less than marked enzyme alterations occur without clinical sympto these nonspecific changes should be evaluated on an individual basis. clinician may wish to continue amrinone and reduce the dosage or disconti the drug based on the usual benefit-to-risk considerations.

HOW SUPPLIED Ampuls of 20 mL sterile, clear yellow solution contain INOCOR 5 mg/mL, box of 5 (NDC 0024-0888-20). Each 1 mL contains INOC lactate equivalent to 5-mg base and 0.25 mg sodium metabisulfite in water injection.

1. Benotti JR, Grossman W, Braunwald E, et al: Effects of amrinone on myocardial energy metabolism and hemodynamics in patients with severe congestive heart failure due to coronary artery disease. *Circulation* 1980;62:28-34.

State-of-the-heart

Inocor® I.V.

(AMRINONE)

Dual-acting therapy, instead of catecholamines

Winthrop PHARMACEUTICALS

Winthrop Pharmaceutic
Division of Sterling Drug
New York, NY 10

71013 Printed in USA March 1987

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

THE B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

1987 AWARDS

At the IARS 61st Congress in March of 1987, the Board of Trustees announced recipients of the 1987 Award as follows:

Bruce A. Bollen, MD, University of Iowa College of Medicine, Iowa City, IA:
"The Role of Arterial Diameter, Vascular Endothelium and Activator Ca^{++} *in Coronary Smooth Muscle Response to Halothane and Isoflurane"*

Robert Forbes, MD, and **David J. Murray, MD,** University of Iowa College of Medicine, Iowa City, IA:
"Development of a Program to Assess Clinical Performance of Resident Physicians in Anesthesia"

Mervyn Maze, MB, ChB, Stanford University School of Medicine, Stanford, CA:
"Anesthetic Depth and Central Monoaminergic Transmission"

John Christopher Sill, MB, BS, Mayo Foundation, Rochester, MN:
"Inhalational Anesthetics and Coronary Vasomotion"

1988 B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

Applications for up to $25,000 are invited for the 1988 Award, subject to the following basic conditions:

- The proposal must be within the general field of anesthesiology and may be for research, clinical care, education, or administration.
- The applicant must be a member of the International Anesthesia Research Society.
- Applications must be received in the IARS Cleveland office no later than **December 8, 1987.**
- The official application for the Award must be used. This form, as well as the guidelines for applicants, is available on request to:

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, OH 44122
Telephone: (216) 295-1124

The 1988 Award(s) will be announced at the Annual Scientific Meeting (62nd Congress) of the International Anesthesia Research Society to be held at the Hotel Inter-Continental, San Diego, California, March 5-9, 1988.

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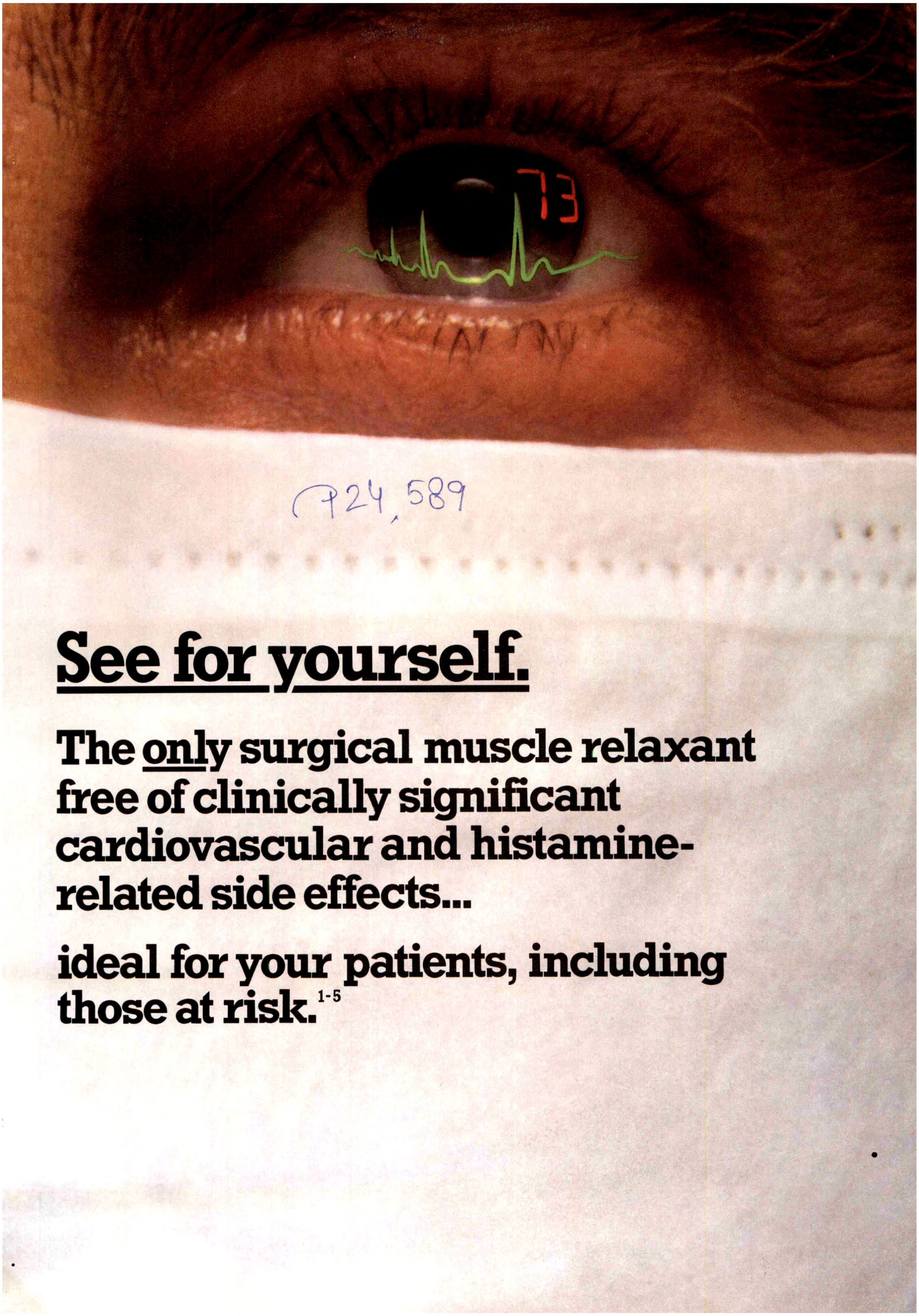
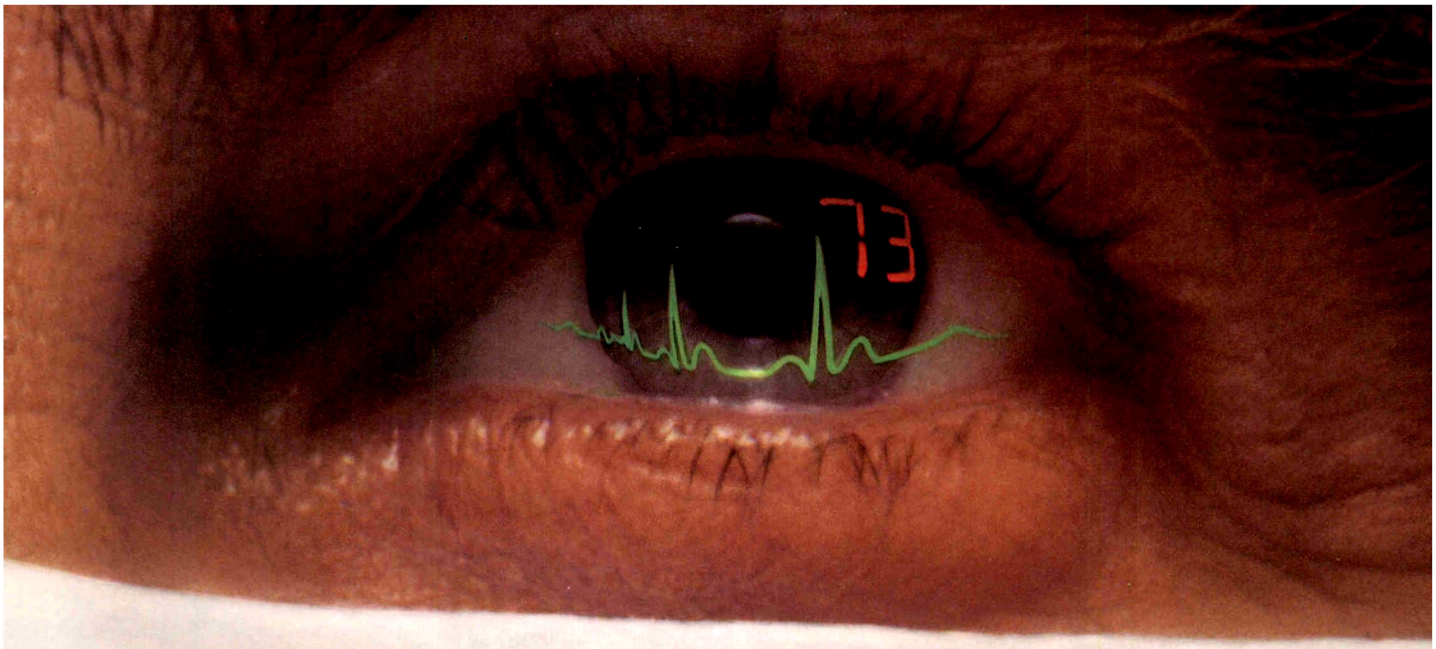
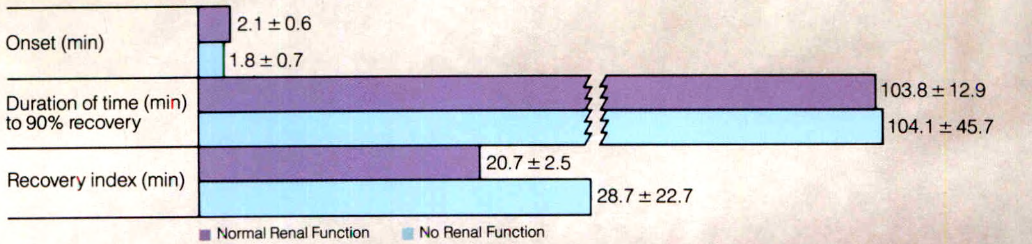

73
See for yourself.
The only surgical muscle relaxant free of clinically significant cardiovascular and histamine-related side effects...
ideal for your patients, including those at risk.[1-5]



Performance unaffected by renal function.[6]

Despite administration of high doses of NORCURON®, no significant differences in onset time, duration of action, or recovery index have been noted between patients with and without renal function.[6]

Comparative Indices of Neuromuscular Blockade for Patients With and Without Renal Function Given Equal Doses (0.14 mg/kg)* of NORCURON® (vecuronium bromide) by Bolus Injection†



Although high doses of NORCURON® were used to assess its pharmacokinetics, it is recommended that the initial dose not exceed 0.08 to 0.1 mg/kg.
† Adapted from Miller et al.[6]

The surgical muscle relaxant ideal for virtually all patients including those at risk.

Norcuron®
(vecuronium bromide) injection

See full prescribing information on following page.

References: 1. Morris RB, et al: The cardiovascular effects of vecuronium (ORG NC 45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1983; 58:438-440. **2.** Durant NN: Norcuron®—a new nondepolarizing neuromuscular blocking agent. *Semin Anesth* 1982; 1:47-56. **3.** Krieg N, Crul JF, Booij LH: Relative potency of ORG NC 45, pancuronium, alcuronium, and tubocurarine in anesthetized man. *Br J Anaesth* 1980; 52:783-787. **4.** Gallo JA, et al: Hemodynamic effects of bolus injection of vecuronium in cardiac surgical patients. *Anesthesiology* 1984; 61:A63. **5.** Basta SJ, et al: Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiology* 1983; 59:A273. **6.** Miller RD, et al: Pharmacokinetics of vecuronium in patients with kidney disease, in Agoston S, et al (eds): *Clinical Experiences with Norcuron (ORG NC 45, Vecuronium Bromide).* Amsterdam, Excerpta Medica, 1983, p 124.

Norcuron® (vecuronium bromide) injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: NORCURON® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2β 3α, 5α, 16β, 17β)-3, 17-bis(acetyloxy)-2-(1-piperidinyl)androstan-16-yl]-1-methyl-, bromide.

Norcuron® is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

CLINICAL PHARMACOLOGY: Norcuron® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about ⅓ more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron® doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED_{90} (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® may be decreased by approximately 15% (see DOSAGE AND ADMINISTRATION section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the neuromuscular block produced by Norcuron® is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron® induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

Pharmacokinetics: At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron® varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron® (vecuronium bromide) injection has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

NO REFRIGERATION REQUIRED

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron®; equipotent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron®. Limited data derived from patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary capillary wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease). Limited clinical experience (3 patients) with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

INDICATIONS AND USAGE: Norcuron® is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: None known.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: Renal Failure: Norcuron® is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTANT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

Norcuron® has no known effect on consciousness, the pain theshold or cerebration. Administration must be accompanied by adequate anesthesia.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY). The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®; therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron® during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

OVERDOSAGE: There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION: Norcuron® (vecuronium bromide) injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution
5% glucose in saline
5% glucose in water
Lactated Ringer's

HOW SUPPLIED: 5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile water for injection as the diluent. Boxes of 10 (NDC#0052-0442-17).

5 ml vials (contains 10 mg of active ingredient) only. DILUENT (Sterile Water for Injection, USP) NOT SUPPLIED. Boxes of 10 (NDC#0052-0442-57).

STORAGE: PROTECT FROM LIGHT. Store at 15°-30°C (59°-86°F).

AFTER RECONSTITUTION: Solution may be stored in refrigerator or kept at room temperature not to exceed 30°C (86°F). DISCARD SOLUTION AFTER 24 HOURS. DISCARD UNUSED PORTION. SINGLE USE VIALS.

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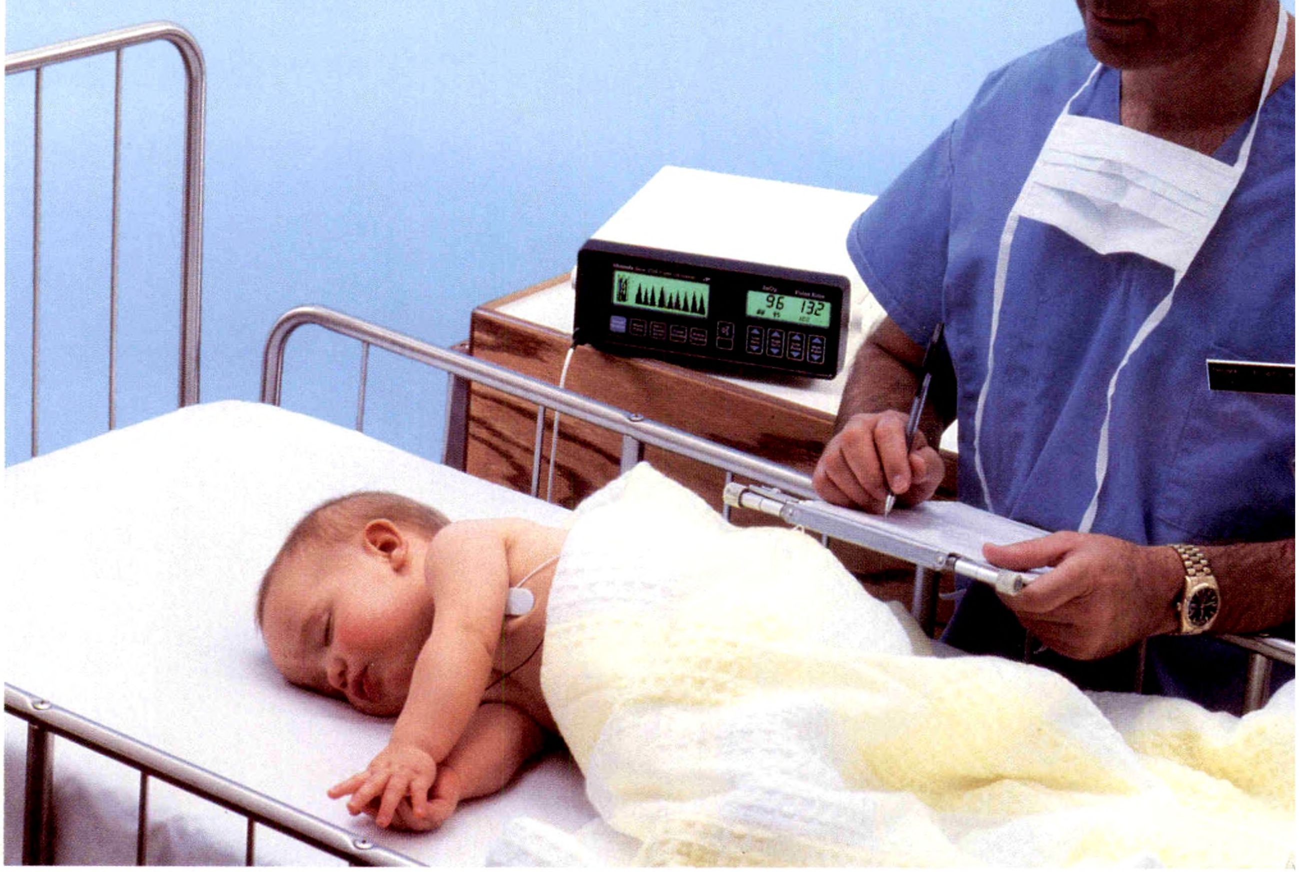

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 Form #E002

Epidural Anesthesia with Bupivacaine:
Effects of Age on Neural Blockade and Pharmacokinetics

Bernadette Th. Veering, MD, Anton G. L. Burm, PhD, Jack W. van Kleef, MD, PhD, Pim J. Hennis, MD, PhD, and Johan Spierdijk, MD, PhD, FFARCS (Hon)

VEERING BTh, BURM AGL, VAN KLEEF JW, HENNIS PJ, SPIERDIJK J. Epidural anesthesia with bupivacaine—Effects of age on neural blockade and pharmacokinetics. Anesth Analg 1987;66:589–93.

Effects of aging after epidural administration of 0.5% bupivacaine without epinephrine were studied in two groups of patients, between 20 and 55 yr old and older than 55 yr, respectively. All patients received 95 mg bupivacaine HCl. The onset of analgesia in caudad segments decreased with age and the upper level of analgesia increased with age. Effects of age on duration of anesthesia could not be demonstrated. The total plasma clearance of bupivacaine decreased and the terminal half-life increased with age. Age had no effect on the peak plasma concentrations and time to peak concentrations.

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—effects of age. ANESTHETICS, LOCAL—bupivacaine. PHARMACOKINETICS—bupivacaine, effects of age.

Age influences the analgesic spread after epidural administration of local anesthetic agents. However, discrepancies exist between studies that have evaluated the extent of the influence of age on the analgesic spread. Some investigators found a slight increase in the extent of analgesic spread with age after administration of a fixed volume of a local anesthetic agent (1–3). Others found that the influence of age on the dose–response relationship varies with different volumes and emphasizes interindividual variability (4–7). In addition, the influence of aging on the duration of the neural blockade has been poorly investigated.

Effects of aging on the pharmacokinetics of local anesthetics have not been studied extensively. Abernethy and Greenblatt (8) and Cusson et al. (9) investigated the effects of age on the pharmacokinetics of lidocaine after intravenous administration. Their studies demonstrated a marked decrease in the plasma clearance and a marked increase in the elimination half-life in elderly persons compared with young male volunteers and patients. Interestingly, such changes could not be demonstrated in female subjects (8). Freund et al. (10) studied the effects of age on the plasma concentrations after caudal administration of lidocaine and bupivacaine. They were unable to demonstrate any effects of age, but meaningful evaluation of the effects on clearance was not possible because of the short sampling times.

In this study, the effects of age on both the quality and the duration of the epidural blockade, as well as on the plasma concentration profiles, were investigated after epidural administration of bupivacaine.

Patients and Methods

After approval by the Committee on Medical Ethics of the University Hospital and obtaining informed consent, two groups of patients (ASA status 1 or 2) scheduled for minor orthopedic, urological, or lower abdominal surgery were studied. Patients in group 1 were 20–55 yr old and patients in group 2 were older than 55 yr (Table 1). None of the patients had diabetes or a history of neurological diseases or bleeding diathesis, or was suffering from peripheral arteriosclerosis.

Premedication consisted of lorazepam, 1–2 mg sublingually, 1.5 hr, and atropine, 0.25–0.5 mg intramusculary, 45 min before induction of epidural anesthesia. A rapid intravenous infusion of 500 ml dextrose in saline was administered before the epidural injection. Thereafter, the infusion rate was maintained at 2 $ml^{-1} \cdot kg^{-1} \cdot hr^{-1}$. A central venous catheter was introduced into the superior vena cava via the basilic or the cephalic vein after local infiltration with lido-

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Table 1. Patient Characteristics*

	Group 1 (20–55 yr)	Group 2 (> 55 yr)
Number of patients	15	15
Number of females	4	2
Age (yr)	36 ± 11	70 ± 8
(Range)	(21–54)	(56–84)
Weight (kg)	73 ± 12	76 ± 11
(Range)	(53–85)	(52–88)
Height (cm)	177 ± 11	174 ± 6
(Range)	(160–189)	(164–184)

*Data are mean ± SD.

caine 0.5%, the catheter being advanced until the tip was located at least 6 cm proximal to the junction of the azygos vein and the superior vena cava. The correct location of the catheter tip was verified by roentgenograms of the thorax.

After local infiltration of the skin with lidocaine 0.5%, a modified 18-gauge Hustead needle was inserted into the epidural space using a midline approach at the L3–4 interspace. During the procedure, the patient was lying in the lateral position. An air-filled syringe was used for detection of the loss of resistance to identify the epidural space. With the bevel of the needle pointing cephalad, a test dose of 2 ml bupivacaine 0.5% with epinephrine 1:200.000 was injected and 3 min later 17 ml bupivacaine 0.5% without epinephrine was administered at a rate of 1 ml/sec. After the injection, the patient was turned to the supine horizontal position.

During the operation, no sedatives were administered. Arterial blood pressure (sphygmomanometer) and heart rate (from the ECG) were monitored during the anesthesia procedure and the operation itself and in the recovery room. If the systolic blood pressure decreased more than 30% or below 100 mm Hg, ephedrine 5 mg was given intravenously.

Analgesia was assessed and defined as absence of pain to pinprick. Motor block of the lower extremities determined bilaterally using a modified Bromage classification was rated from 0 to 3 (0, = full flexion of knee and foot; 1, = just able to move knee; 2, = able to move foot only; 3, = unable to move foot). The results obtained for both extremities were added, giving a maximum score of 6 (complete motor blockade). Assessments were made every 5 min during the first 30 min after the injection, then at 15-min intervals until complete recovery. The following values were calculated:

- The time to initial onset of analgesia at the L1–L2 dermatomes.
- The time to initial onset of motor blockade.
- The time until maximum cephalad spread of analgesia.
- The time until maximum caudad spread of analgesia.
- The highest level of analgesia.
- The maximum number of segments blocked.
- The maximum score of motor block.
- The time until the level of analgesia had receded two segments.
- The time until recovery of analgesia at the T12 dermatome.
- The time until total disappearance of analgesia.
- The time until total recovery from motor blockade.

Central venous blood samples (5 ml) were collected before the epidural injection and 5, 10, 15, 20, 25, 30, 35, 40, 50, 60, 90, 120, 150, 240, 360, 480, 600, 720, 960, 1200, and 1440 min after injection. Plasma was separated by centrifugation at 2.500 *g*, stored at −20°C, and assayed for bupivacaine using a capillary gas chromatographic method with a coefficient of variation less than 6% (11). The individual peak plasma concentrations (C_{max}) of bupivacaine and the time at which these were reached (t_{max}) were determined. Terminal half-lives ($t_{1/2,Z}$) were calculated from the rate constants (K_Z) obtained by linear regression analysis of the log-linear part of the plasma concentration vs time curve:

$$t_{½,Z} = 0.69/K_Z.$$

The area under the plasma concentration–time curve (AUC) was determined using the linear trapezoidal rule, including extrapolation to infinity. The mean plasma clearance (CL) was calculated according to the following equation:

$$CL = D/AUC$$

where D is the administered dose.

Statistical comparisons were done using the Mann-Whitney U-test. The relationships between variables of the neural blockade and age and between pharmacokinetic parameters and age were determined using linear regression and correlation analysis. A *P* value of less than 0.05 was considered statistically significant. Values were expressed as mean ± SD.

Results

Satisfactory blocks were obtained in all patients. One young and one older patient received atropine within 30 min after administration of the local anesthetic because of bradycardia (heart rate below 60 beats/min)

Table 2. Characteristics of Neural Blockade after Epidural Administration of 0.5% Bupivacaine[a]

	Group 1 (n = 15)	Group 2 (n = 15)
Analgesia		
Initial onset time (min)	6.2 ± 2.0	5.3 ± 2.4
Time to maximal cephalad spread (min)	21.8 ± 7.7	27.0 ± 7.0
Time to maximal caudad spread (min)	22.8 ± 7.5	15.7 ± 5.3[b]
Maximal number of segments blocked	13.8 ± 2.8	16.3 ± 2.7[c]
Highest level (T dermatome)	9.1 ± 2.9	6.7 ± 2.6[c]
Duration highest level (min)	116 ± 45	100 ± 28
Two-segment regression (min)	156 ± 59	123 ± 31
Time to recovery at T_{12} (min)	170 ± 74	204 ± 68
Time to total recovery (min)	395 ± 106	405 ± 70
Motor blockade		
Initial onset time (min)	15.9 ± 6.5	13.1 ± 6.3
Maximum degree of block	4.2 ± 1.5	4.5 ± 1.4
Time to total recovery (min)	288 ± 107	264 ± 85

[a]Values are mean ± SD.
[b]Differences between group 1 and group 2: $P < 0.02$.
[c]Differences between group 1 and group 2: $P < 0.05$.

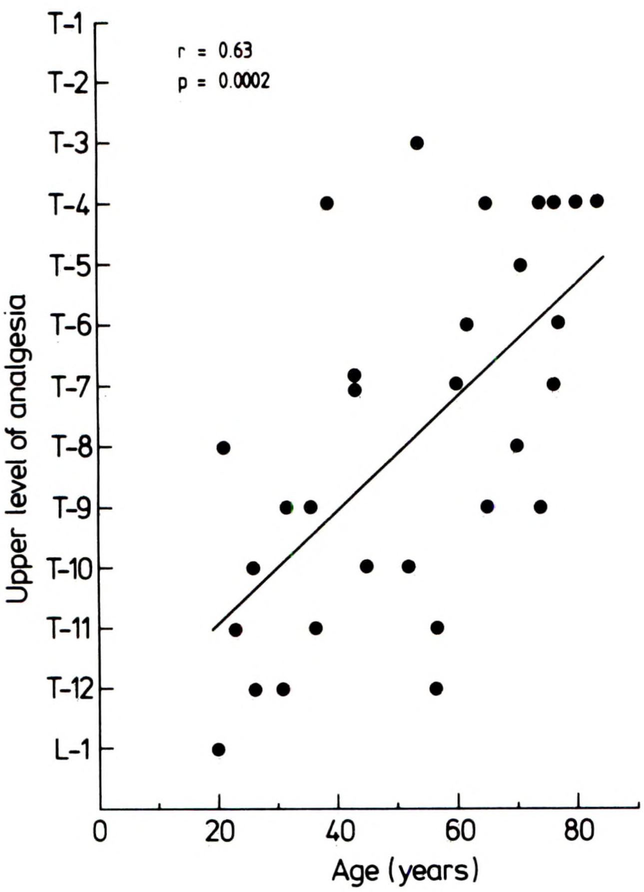

Figure 1. Relationship between the upper level of analgesia and age after epidural administration of bupivacaine 0.5%.

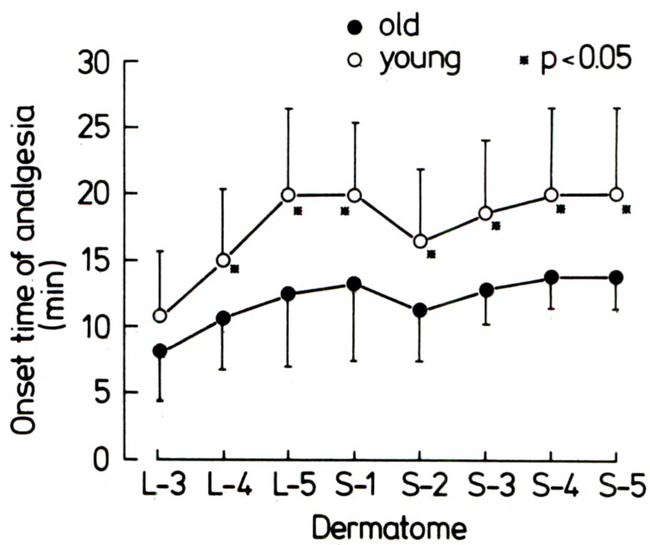

Figure 2. Mean onset times of the caudad segments in the young and old patient groups after epidural administration of bupivacaine 0.5%.

developed. Ephedrine 5 mg was given intravenously to four older patients when systolic blood pressure decreased more than 30%; the lowest systolic blood pressure was never below 90 mm Hg. The mean percentage decrease from control systolic and diastolic blood pressure during the first hour did not exceed 10% in both groups.

In all patients, bilaterally equal epidural blocks were obtained: no patient developed a block that varied more than one segment between the two sides of the body. The characteristics of the neural blockade in both groups are summarized in Table 2. In the older patients, the upper levels of analgesia were higher ($P < 0.05$). There was a moderate correlation between the maximal height of analgesia and the age of the patients (r = 0.63, P = 0.0002, Fig. 1). The time to maximal caudad spread was shorter in the older pa-

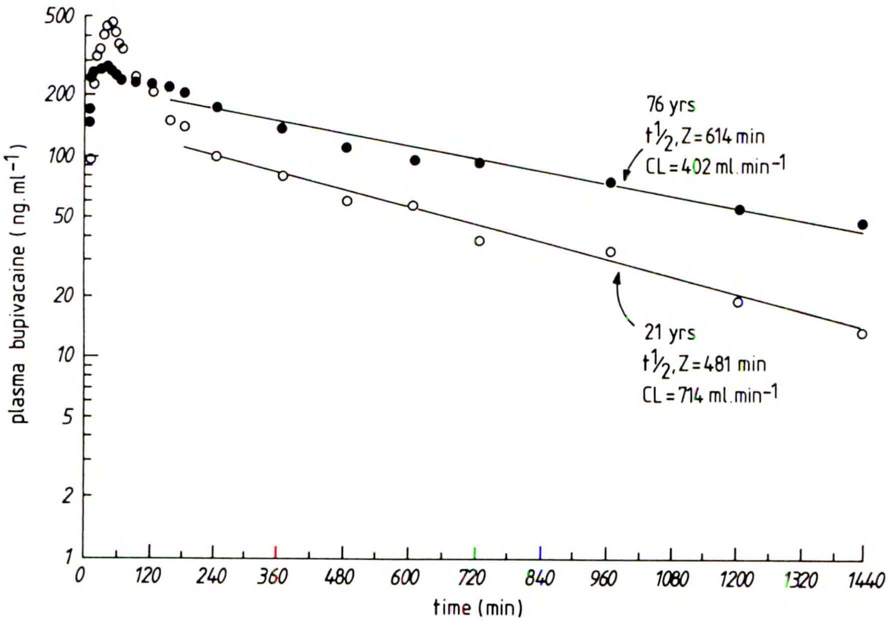

Figure 3. Representative plasma concentrations profiles after epidural administration of bupivacaine 0.5% in a young and an old patient.

Table 3. Pharmacokinetic Data Obtained after Epidural Administration of 0.5% Bupivacaine[a]

	Group 1 (n = 14)	Group 2 (n = 14)
t_{max} (min)	20 ± 10	26 ± 14
C_{max} (μg/ml)	0.53 ± 0.15	0.47 ± 0.12
$t_{1/2,Z}$ (min)	457 ± 96	585 ± 156[b]
CL (ml/min)	514 ± 150	332 ± 93[c]

[a]Values are mean ± SD.
[b]Differences between group 1 and group 2: $P < 0.02$.
[c]Differences between group 1 and group 2: $P < 0.001$.

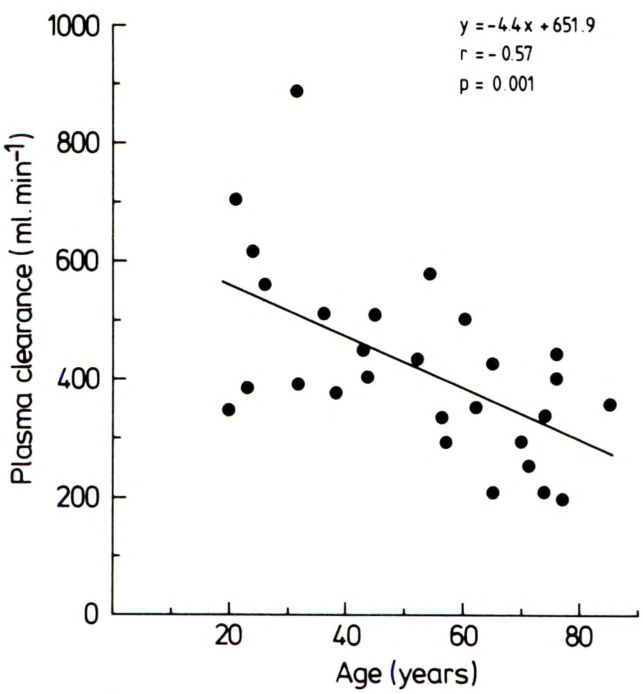

Figure 4. Relationship between total plasma clearance and age.

tient group ($P < 0.02$), as were the times of onset of analgesia at L_4, L_5 and the sacral segments ($P < 0.01$, Fig. 2).

Age did not influence the rate of regression of analgesia or the total time for recovery from analgesia. Neither could age be shown to affect the degree or time to recovery from motor blockade.

Two patients were excluded from the pharmacokinetic analysis, one young patient (36 yr) and one older patient (80 yr) who had outlier peak plasma levels of 1.75 μg/ml and 1.61 μg/ml, respectively; the corresponding peak time was 5 min for both patients. In these patients, there was no clinical evidence of local anesthetic toxicity and both patients had a good quality of analgesia and motor blockade. Figure 3 shows a representative example of plasma concentration vs time curves for an older and a younger patient.

The results of the pharmacokinetic analysis are shown in Table 3. Peak plasma concentrations were similar in both groups, as were the corresponding peak times. The terminal half-life was prolonged in the older patients ($P < 0.02$). The total plasma clearance was much lower in the older patients ($P < 0.001$). There was a moderate inverse correlation between total plasma clearance and age ($r = -0.57$, $P = 0.001$, Fig. 4.).

Discussion

The effect of age on the extent of spread of analgesia in the present study agrees with other reports in which comparisons were made after administration of a fixed volume (1–3). However, the magnitude of this effect is small. Several factors may contribute to the more extensive spread in the elderly. In older patients, lateral escape of the local anesthetic solution is minimal, due to the sclerotic intervertebral foramina. This favors longitudinal spread (12). Moreover, with aging the neural population declines steadily within the spinal cord. This could make the older patients more sensitive to local anesthetics, which is probably (partially) the cause of the more rapid time of onset of analgesia in caudad segments in older patients (Fig. 2). In addition to the changes mentioned, we have demonstrated that age does not influence duration of the neural blockade.

The results of the pharmacokinetic part of the study suggest that age has minimal, if any, effect on the peak plasma concentration and the corresponding peak time after epidural administration of bupivacaine. These results confirm the observations of Freund et al. (10), who also found that the interindividual variability in the peak plasma concentration is more impressive than the effect of age on these parameters. Our data demonstrate a marked effect of age on the clearance and a moderate effect on the terminal half-life of bupivacaine. The reduction in the clearance of bupivacaine resembles the reduction in the clearance of lidocaine demonstrated by Abernethy and Greenblatt (8) and by Cusson et al. (9), although other investigators have reported that the clearance of lidocaine in both humans and rhesus monkeys does not change with age (13–14). The age-dependent prolongation of the terminal half-life is difficult to interpret. In young subjects, this parameter is mainly dependent upon the rate of absorption of bupivacaine from the epidural space into the general circulation (15–16). A prolongation of the terminal half-life therefore may be due to a slowing of absorption. However, changes in the systemic disposition (volume of distribution and clearance) may also contribute to the prolongation. If the prolongation of the half-life is due to a slowing of the absorption, this appears not to be accompanied by an increase in the duration of action.

The significance of our findings in terms of systemic toxicity are difficult to determine. Certainly the peak plasma concentrations after epidural administration of a single fixed bupivacaine dose are similar in older and in younger patients. On the other hand, the markedly reduced clearance and the prolonged terminal half-life indicate that in older patients a more extensive systemic accumulation of bupivacaine may occur after intermittent injection or during continuous epidural infusion of bupivacaine. However, this does not necessarily mean that the potential for systemic toxicity is also age dependent, since the toxic threshold concentrations may alter with age.

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Incomplete Reversal of Pancuronium Neuromuscular Blockade by Neostigmine, Pyridostigmine, and Edrophonium

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BARTKOWSKI RR. Incomplete reversal of pancuronium neuromuscular blockade by neostigmine, pyridostigmine, and edrophonium. Anesth Analg 1987;66:594–8.

Three clinically used anticholinesterases—neostigmine, pyridostigmine, and edrophonium—were tested for their ability to reverse two levels (60% and 95%) of neuromuscular blockade produced by pancuronium. A controlled in vitro environment of the rat diaphragm–phrenic nerve system was used for the studies. Concentrations of anticholinesterases spanned the clinical range and were extended beyond to establish dose–response curves. Neostigmine was the most potent reversal drug (ED_{50} for 95% block 5.5 ± 4 nM), followed by pyridostigmine (0.27 ± 0.06 μM) and edrophonium (2.1 ± 0.05 μM). The three drugs were equally effective at reversal of block and fade as measured by train-of-four stimulation. The dose-response curves for all three drugs showed a ceiling effect for reversal of tension and fade. Supraclinical concentrations of drug did not effect complete reversal, especially at 95% block. High concentrations of anticholinesterase led to randomly appearing hyperactivity manifested by spontaneous twitching and repetitive firing with severe fade on stimulation.

Key Words: ANTAGONISTS, NEUROMUSCULAR RELAXANTS—neostigmine, pyridostigmine, edrophonium. NEUROMUSCULAR RELAXANTS—pancuronium.

Because three anticholinesterase drugs are available for clinical use, we constructed an experiment to compare their potency and effectiveness in a controlled laboratory setting. Using the perfused rat hemidiaphragm, neostigmine, pyridostigmine, and edrophonium were tested for their ability to reverse the neuromuscular block produced by pancuronium. This experiment was also framed to test two areas beyond the reach of the usual clinical study. The first was to test the effects of anticholinesterase concentrations much greater than those used clinically. The second was to test the ability of these drugs to reverse a profound block (95% twitch suppression) in a range where reversal is prolonged or difficult (1,2). The experiment also tested edrophonium against the more established agents because of questions that have arisen concerning the efficacy of this drug (3).

Methods and Materials

The left hemidiaphragm and phrenic nerve from male Wistar rats (300–500 g) were dissected free immediately following decapitation and mounted on the measurement apparatus. There, while temperature was maintained at 37°C, peak developed tension was measured after stimulation of the phrenic nerve. Nutrition and oxygen were supplied to the muscle via perfusion through the phrenic vein with a solution designed to provide levels of ions including calcium and magnesium in the normal range for rats and humans. Details of the apparatus, perfusion, and measurement system have been described previously (4). The stimulus pattern for these experiments consisted of four nerve stimuli separated by 0.5 sec (train of four). The train was repeated at one-min intervals. Tension values for the first pulse of the train were used to determine twitch height suppression while the ratio of the fourth to the first was noted as the train-of-four ratio.

Experimental Plan

After a stable tension was achieved for 10 min by perfusion at 37°C, a dose–response curve was determined for each preparation by infusing multiple (three to six) concentrations of pancuronium until equilibration was reached. Concentrations that provided a single twitch tension near 40% and 5% of the drug-free tension were selected from the dose–response results. Then the 40% or 5% concentration of pancuronium was infused alternately while a single anticholines-

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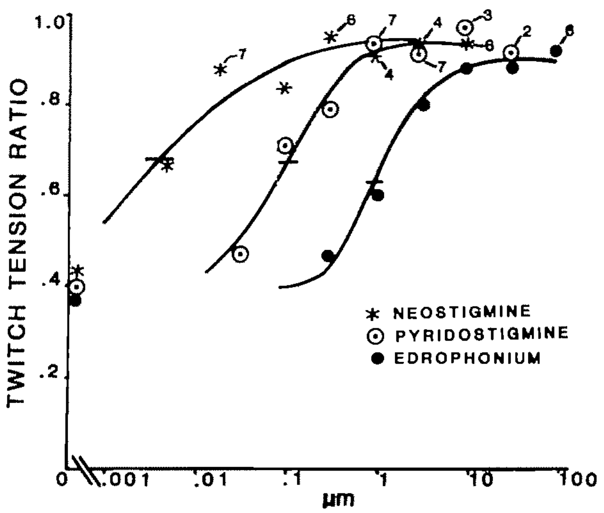

Figure 1. Single twitch ratio (force/control) during reversal by increasing concentrations of neostigmine, pyridostigmine, or edrophonium. Initial twitch ratio (no reversal) was nominally 0.4. Curves are best fit by probit analysis showing ED_{50} and standard error as a horizontal bar. Numbers at a data point mark points representing fewer than eight experiments (see text).

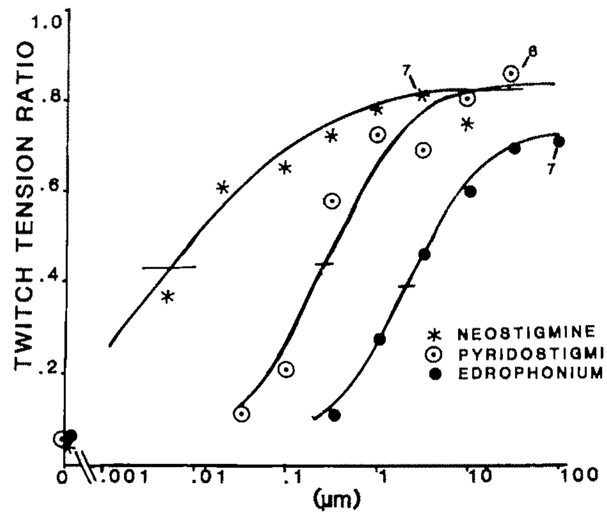

Figure 2. Single twitch ratio (force/control) during reversal from a nominal initial ratio of 0.05. Curves are best fit by probit analysis showing ED_{50} and standard error by a horizontal bar. Numbers included on graph mark points representing fewer than eight experiments (see text).

terase (neostigmine, pyridostigmine, or edrophonium) was added to the perfusate in increasing concentration. The concentrations employed were neostigmine—0, 5, 20, 100, 300, 1000, 3000, and 10,000 nM; pyridostigmine—0, 0.03, 0.1, 0.3, 1.0, 3.0, 10, and 30 μM; and edrophonium—0, 0.3, 1, 3, 10, 30, and 100 μM. Each preparation was perfused with only one anticholinesterase. During the experiments, all the above concentrations of that anticholinesterase were tested at both the 40% and 5% initial twitch levels.

The experiments were begun at the lowest concentration of anticholinesterase. Half of the preparations were started at the high and half at the low pancuronium concentration. Both pancuronium and anticholinesterase were added to the perfusate so their introduction was simultaneous during each measurement. At each concentration of anticholinesterase, the two pancuronium concentrations were tested in alternating fashion. In this way, only one drug concentration, either pancuronium or reversal, was changed between measurements. After each two concentrations of anticholinesterase, the drug-free baseline-evoked twitch height was retested by washout with perfusion solution (10–20 min) to achieve a tension stable for 5 min. During the washout, a small concentration of pancuronium (one-half to one-third of the 40% tension value) was added to the perfusate to prevent spontaneous activity and repetitive twitching of the muscle due to cholinergic overstimulation, which was observed particularly at the higher concentrations of anticholinesterases. This concentration suppressed spontaneous activity while depressing measured tension less than 3%. Because of the possibility of residual anticholinesterase interfering with interpretation, the level of block was not retested. The pancuronium concentrations chosen at the beginning were used throughout. The entire procedure was performed in a similar fashion for each of the three anticholinesterases.

A total of 24 diaphragm preparations was studied, eight for each of the three anticholinesterases. The perfusion rate for the studies was set at 1.9 ml/min. This produced a stable equilibrium tension—that is, one that remained unchanged for 3 min—within 8–13 min after changing the concentration of pancuronium, anticholinesterase, or both. The one exception was the lowest concentration of neostigmine, 5 nM. When this concentration of neostigmine and the initial concentration of pancuronium were added to the drug-free baseline state, equilibrium took 21–26 min and showed a two-phase response: an initial decrease in tension for 10 min followed by a gradual rise to a stable value. All other anticholinesterase–pancuronium solutions had a single-phase response: the tension moved progressively toward the final equilibrium value.

Data Analysis

The initial step in the analysis was calculation of the ED_{50} for each of the anticholinesterases. For each of the two concentrations of pancuronium, a

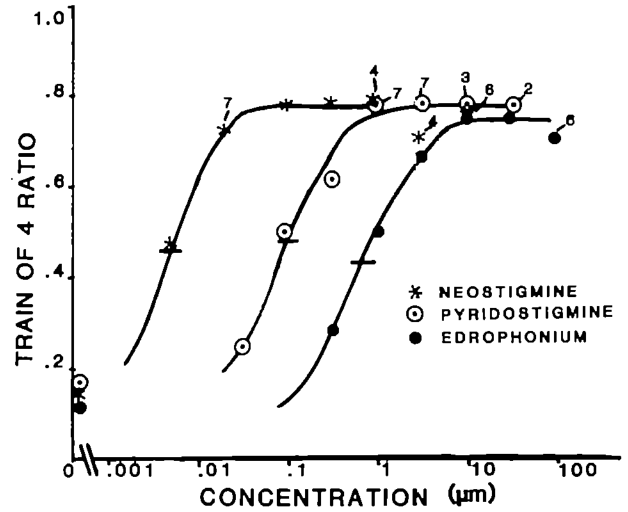

Figure 3. Train-of-four ratio (fourth tension/first twitch tension) during reversal from a nominal initial twitch ratio of 0.4. These data correspond to those in Figure 1. Curves are best fit by probit analysis showing ED_{50} and standard error by a horizontal bar. Numbers on curves, as in Figure 1, indicate whether fewer than eight experiments are included at a point.

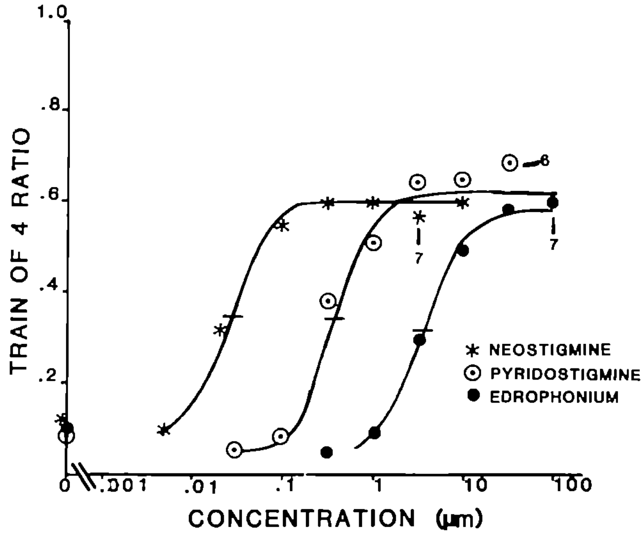

Figure 4. Train-of-four ratio during reversal from a nominal initial twitch ratio of 0.05. These data correspond to those in Figure 2. Curves are best fit by probit analysis showing ED_{50} for train-of-four reversal and its standard error as a horizontal bar. Numbers on curves are the same as in Figure 2 and indicate whether fewer than eight experiments are included at a point.

dose–response curve was constructed from the first twitch tension data and the anticholinesterase dose. Using the probit method of Finney (5) an ED_{50} was obtained as the average dose required to return the tensions 50% of the distance to the maximum or plateau tension obtained during reversal. In this manner, six values for ED_{50} could be obtained, one for each of three anticholinesterases at each of two levels of neuromuscular block. This procedure was repeated for the train-of-four ratios for all experiments yielding six more ED_{50} values.

For further analysis, the dose–response curves were normalized so that they were expressed in terms of an ED_{50}. In this way, the three anticholinesterase dose–response curves could be expressed on a common scale. This was done for twitch tension and train-of-four ratio at both levels of block. The three drugs were then compared by analysis of variance for repeated measurement with $P < 0.05$ chosen as the level of statistical significance.

Results

The results are shown graphically in Figures 1–4 and numerically in Table 1. Figures 1 and 2 display the relative tension of the first twitch from the fully suppressed value, nominally 40% (Fig. 1) and 5% (Fig. 2) of peak, to the values at maximal anticholinesterase concentration. All values for an individual curve are taken at the same concentration of pancuronium. The curves thus represent equilibrium values of tension at a fixed pancuronium value while antagonism via anticholinesterase increases. At the higher anticholinesterase concentrations, signs of cholinergic hyperactivity were sometimes observed. These included spontaneous fasciculations of the diaphragm associated with repetitive firing on stimulation. When this was observed, measured values of twitch tension were greater than the control, as much as 1.9 times control value. These were associated with train-of-four fade greater than that for the normally behaving preparations at that concentration. Values representing overstimulation were removed from the analyzed curves. This phenomenon is represented in the figures by the number next to a symbol, if that symbol represents less than eight diaphragms. This phenomenon was more prevalent at the lower pancuronium concentration, as can be seen from the figures. Best-fit curves through the points were drawn using probit analysis and are displayed. The ED_{50} and its standard error are also shown.

The train-of-four ratio was treated in an identical manner. Results from the experiments and analysis are displayed in Figures 3 and 4. Again, points showing cholinergic hyperactivity were not included in the curve fit. ED_{50} values calculated from the data are shown on the curve and in the table along with their associated standard errors. The slope of the dose–response curves as determined by probit analysis are not significantly different (see Table 1). The dose–response curves can be considered parallel within

Table 1. Potency Data for Reversal Drugs

Drug	Initial twitch % of control	Twitch		Train-of-four	
		ED_{50}[a]	Slope[b]	ED_{50}[a]	Slope[b]
Neostigmine	40	4.4 ± 2.8	0.98 ± 0.23	5.0 ± 1.9	2.36 ± 0.81
Neostigmine	5	5.5 ± 4.0	0.77 ± 0.16	25.9 ± 7.0	2.79 ± 0.66
Pyridostigmine	40	0.10 ± 0.02	1.69 ± 0.25	0.10 ± 0.03	2.03 ± 0.47
Pyridostigmine	5	0.27 ± 0.06	1.32 ± 0.17	0.37 ± 0.08	2.68 ± 0.58
Edrophonium	40	0.97 ± 0.17	2.02 ± 0.32	0.69 ± 0.27	1.88 ± 0.46
Edrophonium	5	2.1 ± 0.5	1.37 ± 0.19	3.5 ± 0.8	2.54 ± 0.51

Values are means ± standard error as determined by probit analysis. Each value is computed from eight experiments. Points reflecting cholinergic hyperactivity are excluded (see text).
[a]ED_{50} expressed in nM for neostigmine, in μM for others.
[b]Probit units/log dose.

the precision of the data. This is convenient for comparison of relative potency since the potency ratio among the three reversal drugs will then be constant over the entire dose range.

Within the confidence limits for ED_{50} values (Table 1), the tension data for all three reversal drugs could be expressed at five distinct concentrations: control, ED_{50} (40% tension), ten times ED_{50}, 30 times ED_{50}, and 100 times ED_{50}. The data for all experiments displayed in Figures 1–4 were subjected to a three-way nested design analysis of variance (6) to determine if any differences could be found among the drugs when each is given at the same relative concentration. Unlike the data displayed in the figures where some points were excluded, all points were entered, including those representing hyperactivity, i.e., tension ratios above one, so that even this property was compared. The analysis found no differences at either the 40% or 5% level in the efficacy of any of the drugs—the peak reversal effect for twitch tension or train-of-four ratio. One comparison reached statistical significance. That was the comparison of reversal from 5% of initial tension for the first twitch. The neostigmine increase from control to ED_{50} concentration at 40% initial tension was significantly greater than that for the other drugs.

Discussion

The three drugs neostigmine, pyridostigmine, and edrophonium are effective pancuronium-reversal agents in the preparation used in the present study. The potencies found in this in vitro study are consistent with clinical human data: neostigmine was found to be the most potent and edrophonium the least potent. A more quantitative comparison of potency with human data is not possible. The data presented here were taken in rat muscle, specifically the diaphragm, whereas most human data are from adductor pollicis. The methodologies employed to measure potency or ED_{50} are also not comparable. In the rat diaphragm experiments, pancuronium concentrations were held constant and equilibrated with a fixed concentration of reversal agent. Clinical reversal employs a bolus dose of reversal agent, leading to an unknown and changing drug concentration at the site of action. In spite of these differences, however, the relative potencies agree.

A more interesting facet of the study is the extension of dose–response data to values above the ED_{90}. Inspection of the dose–response curves for tension and train-of-four ratio shows a ceiling or plateau effect for reversal. The efficacy of these drugs is thus limited in this preparation. The drugs do not show an unlimited capacity to reverse any effect of pancuronium. At the higher concentration of pancuronium, the maximum reversal attained never meets the train-of-four requirement (above 0.7) for adequate clinical recovery (7). This is not too surprising since reversal is not due to pharmacological antagonism. Simple antagonism would suggest an infinite capability for reversal but that is not the process taking place here. The pharmacologic competition is between pancuronium and acetylcholine at the end-plate receptor of muscle. Anticholinergic drugs are only indirect antagonists by virtue of their inhibition of acetylcholine breakdown. When acetylcholine breakdown by cholinesterase is suppressed, acetylcholine concentrations are still limited by the amount released and alternate elimination paths such as diffusion and reuptake. As the other elimination paths become dominant, we expect no further effect from an anticholinesterase, as was found in these experiments.

A phenomenon seen at the higher concentrations of these three reversal drugs was cholinergic hyperactivity. This was manifested by evoked tensions greater than control. The graphic-tension record often showed small spontaneous twitches in the muscle

that were also visible on its surface. At the same time, the train-of-four ratio decreased from typical values at that concentration. This phenomenon has been described for these drugs (8) and appears to be the basis of recommendations for a maximum clinical dose. In the present experiments, cholinergic excess was sporadic. It occurred at higher concentrations of all three anticholinesterases and was much less pronounced at the higher pancuronium dose. It often occurred at one concentration of anticholinesterase and not at the next higher level in the same diaphragm. To take this into account, these unreliable values were removed from the analysis of dose–response curves. Averaging in a high tension with several low tensions could give an elevated average value and a false impression that reversal was uniformly effective. The aberrant values were included in a separate comparison of the three drugs when all were scaled according to their ED_{50} at 40% tension. This comparison found only one difference among the drugs, namely, the greater increase in tension with neostigmine from control to the ED_{50} value for tension suppressed to the 5% level. This probably reflects more the low confidence in that ED_{50} value and the difficulty of working at such low concentrations of neostigmine than any real difference in activity. As stated in the results, equilibration at the lowest concentration of neostigmine (5 nM) was slower than for any other drug or concentration, so its value is the least reliable. This factor probably accounts for the slight apparent difference in shape of the neostigmine tension dose–response curves. The statistics, however, do not show the curves to be of different shapes because of the variability and associated lower confidence in the slope of the curves.

The difficulty in interpreting the neostigmine data arose from the longer equilibration time observed for the 5 nM neostigmine concentration. The prolonged equilibration could represent restricted or buffered diffusion of drug in the synaptic cleft. Prolongation of equilibration seen for *d*-tubocurarine at the neuromuscular junction (9) was ascribed to this mechanism, which involves repeated binding of a drug to receptors concentrated in a restricted space. Diffusion slows because only unbound drug is free to move. The process is predicted to depend on the drug receptor affinity. The high potency of neostigmine suggests an extremely high receptor affinity, which would lead to a longer equilibration time by this mechanism. At higher concentrations of neostigmine, most cholinesterase binding sites are occupied so the process is less effective. Although we have no direct evidence of restricted diffusion, these observations are consistent with predictions made for this process.

The major findings of this study can be summarized as follows:

1. Neostigmine, pyridostigmine, and edrophonium are equally effective agents in the rat diaphragm preparation for reversal of pancuronium-induced effects on both twitch tension and fade and at high or low concentrations of pancuronium.
2. Anticholinesterases have a ceiling on their efficacy. Higher doses (10 to 100 $\times$ ED_{50}) are not capable of complete reversal of neuromuscular block, especially at the greater levels of blockade.
3. Higher doses of anticholinesterases lead to cholinergic hyperactivity characterized by spontaneous twitching, enhanced twitch tension, and greater fade to multiple stimuli. This hyperactivity is suppressed somewhat by pancuronium and is less frequently seen at higher doses of pancuronium.

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Spinal Cord Blood Flow during Spinal Anesthesia in Dogs:
The Effects of Tetracaine, Epinephrine, Acute Blood Loss, and Hypercapnia

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DOHI S, TAKESHIMA R, NAITO H. Spinal cord blood flow during spinal anesthesia in dogs: the effects of tetracaine, epinephrine, acute blood loss, and hypercapnia. Anesth Analg 1987;66:599–606.

To examine the effects of subarachnoid tetracaine and epinephrine on spinal cord blood flow (SCBF), lumbar SCBF and cerebral blood flow (CBF) were measured simultaneously by the hydrogen clearance technique in dogs (n = 45) anesthetized with halothane. The lumbar subarachnoid administration of tetracaine, 5 mg dissolved in 1 ml of a 7.5% dextrose solution had no significant effect on either SCBF or CBF for 4 hr even though arterial blood pressure and heart rate decreased significantly. After subarachnoid epinephrine alone (100, 300, and 500 μg), SCBF varied widely but did not change significantly with any of the injections, nor did CBF.

Responses of SCBF to hypercapnia and to acute blood loss during spinal anesthesia with tetracaine were also examined. Increased $Pa\text{CO}_2$ (from 35 to 57 mm Hg) increased both SCBF and CBF similarly before and after subarachnoid tetracaine; SCBF increased from 26.8 ± 9.0 ml·100 $g^{-1}\cdot min^{-1}$ (mean ± SD) before to 34.2 ± 13.6 ml·100 $g^{-1}\cdot min^{-1}$ during hypercapnia during spinal anesthesia, which was almost identical to the increase (from 31.5 ± 8.1 ml·100 $g^{-1}\cdot min^{-1}$ to 39.9 ± 6.0 ml·100 $g^{-1}\cdot min^{-1}$) before spinal anesthesia. Whereas acute blood loss (approximately 20% of estimated blood volume) during spinal anesthesia with tetracaine caused a 23% reduction of SCBF ($P < 0.05$), in the absence of tetracaine SCBF remained unchanged during hemorrhagic hypovolemia. These results indicate that subarachnoid epinephrine does not produce a significant reduction in SCBF, though its inclusion with a local anesthetic solution for prolongation of spinal anesthesia has been thought to produce local vasoconstriction. Blood flow to the spinal cord is unlikely to be affected by subarachnoid tetracaine per se under normal conditions. The present study suggests, however, that spinal anesthesia may alter the autoregulatory capacity of SCBF during hypotension due to acute blood loss, but may leave the local blood flow reactivity to respiratory acidosis intact.

Key Words: ANESTHETIC TECHNIQUES—spinal. SPINAL CORD—blood flow.

There are only a few reports (1–8) and several recent abstracts (9–11) dealing with the effects of spinally administered agents on local spinal cord blood flow (SCBF). We previously reported that subarachnoid morphine (1) and lidocaine (2) do not produce statistically significant changes in SCBF in anesthetized dogs whereas subarachnoid phenylephrine in concentrations greater than 0.2% (2) causes a significant decrease in SCBF. Though studied by several investigators (3–7), the effects of epinephrine (200 μg) alone or with a local anesthetic on SCBF are not clear. There are no data concerning the dose-related effects of epinephrine on local SCBF. In addition, like cerebral blood flow (CBF), SCBF has been shown to have an autoregulatory capacity, including significant responses to changes in carbon dioxide tension (12–16). Although our previous studies suggested that subarachnoid morphine and lidocaine may have no effect on autoregulation of SCBF (1,2), this has not been studied sufficiently to determine whether, in the presence of spinal anesthesia, SCBF is able to maintain autoregulation and responses to increased arterial carbon dioxide tensions.

In our present study, we examined the effects of subarachnoid tetracaine and epinephrine on SCBF and CBF in paralyzed, mechanically ventilated anesthetized dogs and SCBF responses to hypercapnia and to acute blood loss in the presence and absence of spinal anesthesia with tetracaine.

Methods

Forty-five unpremedicated mongrel dogs of either sex weighing 6.0–14.0 kg were utilized in this study. All

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animals initially were anesthetized with thiamylal, 10 mg/kg intravenously. Succinylcholine chloride 20 mg was given intramuscularly to facilitate tracheal intubation, followed by an infusion of 20 mg/hr to maintain muscle paralysis. Each dog was ventilated mechanically with a modified T-system using an animal ventilator to maintain end-tidal CO_2 concentration of 4.6 ± 0.3% as measured by a CO_2 analyzer (Normocap, Datex, Finland, or CO_2–O_2 analyzer, Sanei, Tokyo). Anesthesia was maintained with halothane, 1.0–1.5% inspired, oxygen and air. One femoral artery was cannulated for continuous measurement of arterial blood pressure (AP) and to obtain samples for measurements of arterial blood gas tensions and serum electrolyte levels. The ipsilateral femoral vein was cannulated and used for infusion of fluid (lactated Ringer's solution at a rate of 5 $ml{\cdot}kg^{-1}{\cdot}hr^{-1}$) and for administration of sodium bicarbonate if needed to keep the buffer base within normal limits. Esophageal temperature was maintained at 36.5 ± 0.5°C using a heat lamp or ice pads.

The techniques used to measure SCBF and CBF by the hydrogen clearance technique have been described previously (1,2). Briefly, after parietal craniotomy and dorsal laminectomy at L3–5, one electrode (standard wire type, UHE-201) was inserted into the brain and another into the spinal cord through small holes in the dura mater at each site. These electrodes were advanced to a depth of approximately 3–4 mm from the surface of the brain and spinal cord and connected to a hydrogen detecting system (2). In animals that were subjects for the CO_2 inhalation study, two bipolar platinum electrodes (Biomedical Science Co., Tokyo) were used, one for the brain and the other for the lumbar spinal cord. This bipolar electrode was designed to generate hydrogen gas by electrolysis at one part and to detect hydrogen gas by a polarographical method (17,18). A polyethylene catheter, 18-gauge, was inserted into the lumbar subarachnoid space through a small hole in the dura for the subarachnoid administration of drugs. The tip of the catheter was placed approximately 2–3 cm cephalad to the lumbar electrode.

After surgical preparation, each dog was placed in the prone position with the head slightly elevated in order to minimize the gravitational spread of the drugs toward the brain. The inspired halothane concentration was then decreased and maintained at 0.8% with oxygen and air through a modified Ayre's T-tube throughout the remainder of the study. In 12 dogs, cerebrospinal fluid pressure (CSFP) was measured continuously through the subarachnoid catheter (internal volume 0.02 ml), which was filled with a sterile solution of 7.5% dextrose in water (D7.5W). The zero reference point for CSFP was placed at the midthoracic line.

Control measurements of SCBF, CBF, heart rate (HR), AF, and arterial blood gas tensions were made 2 hr after the decrease in the inspired halothane concentration. The 45 animals were divided and subdivided into the following groups:

Tetracaine, 5 mg in 1 ml of 7.5% dextrose in water—16 dogs (two dogs used in previous studies; six also used in the acute blood loss study)

Epinephrine alone: 100 μg—seven dogs
300 μg—seven dogs
500 μg—nine dogs

CO_2 inhalation—seven dogs
(including five dogs given epinephrine, 100 μg, 2 hr previously)

Acute blood loss
Halothane anesthesia alone—six dogs
(including two dogs used later for tetracaine injection after the reinfusion of shed blood)
During spinal tetracaine—six dogs

In 16 dogs (including two dogs used in the blood loss study), 1 ml of tetracaine solution, 0.5% in D7.5W (pH 4.2–4.5), was injected into the subarachnoid space through the catheter, and the measurements were repeated at 30, 60, 120, and 240 min after the injection. In our preliminary investigation, this dose of tetracaine produced complete anesthesia at the T1–5 level that lasted about 110–150 min. In 23 dogs, 1 ml of epinephrine solution (pH 2.60–3.29) 100 μg (n = 7), 300 μg (n = 7), or 500 μg (n = 9), diluted by D7.5W, was injected and followed by the measurements. The effect of D7.5W alone on SCBF is not significant (2).

In order to observe SCBF and CBF responses to hypercapnia during spinal anesthesia, seven dogs (five of which had previously been given epinephrine 100 μg at least 2 hr before) were used. In these dogs, carbon dioxide (7%) was added to inhaled gases before and after subarachnoid tetracaine. Baseline measurements of SCBF and CBF were repeated and followed by measurements made during hypercarbia before and after injection of tetracaine into the subarachnoid space. CSFP was also measured continuously in these dogs.

In six dogs, 20% of estimated blood volume was removed through an arterial line 30–60 min after the subarachnoid injection of tetracaine, and the measurements of SCBF and CBF were repeated after the stabilization of blood pressure in five dogs (excluding one dog that had a cardiac arrest). Six dogs (including two dogs later used for the subarachnoid tetracaine study after reinfusion of shed blood) were used as

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Table 1. Effects of Subarachnoid Epinephrine on SCBF ($ml\cdot 100\ g^{-1}\cdot min^{-1}$), CBF ($ml\cdot 100\ g^{-1}\cdot min^{-1}$), MAP (mm Hg), Mean Values of Hemoglobin (g/100 ml), and Arterial Blood Gas Tensions, pH, and Base Excess (mm Hg, mEq/L) Measurements

Epinephrine	Control				After subarachnoid administration				Arterial blood gas				
	SCBF	CBF	MAP	HR	SCBF	CBF	MAP	HR	Hb	Pa_{O_2}	Pa_{CO_2}	pHa	BE
100 µg (n = 7)	25.8 ± 16.8	52.7 ± 20.0	109 ± 14	126 ± 36	22.9 ± 14.7	54.3 ± 20.2	115 ± 19	139* ± 46	15.0 ± 2.3	224 ± 55	36.2 ± 3.8	7.37 ± 0.05	−4.3 ± 1.1
300 µg (n = 7)	25.1 ± 7.9	47.0 ± 12.6	130 ± 22	125 ± 30	24.0 ± 8.5	47.0 ± 18.1	125 ± 20	137* ± 23	14.3 ± 2.8	208 ± 34	34.8 ± 2.1	7.38 ± 0.06	−3.8 ± 2.9
500 µg (n = 9)	26.7 ± 9.5	52.0 ± 9.5	121 ± 21	123 ± 40	24.1 ± 10.8	51.3 ± 11.5	122 ± 24	141* ± 36	14.8 ± 1.3	227 ± 68	35.3 ± 2.7	7.38 ± 0.03	−3.4 ± 2.0

Abbreviations: SCBF, spinal cord blood flow; CBF, cerebral blood flow; MAP, mean arterial pressure; HR, heart rate; Hb, hemoglobin; BE, base excess.
Each number indicates mean ± SD.
*$P < 0.05$ vs control.

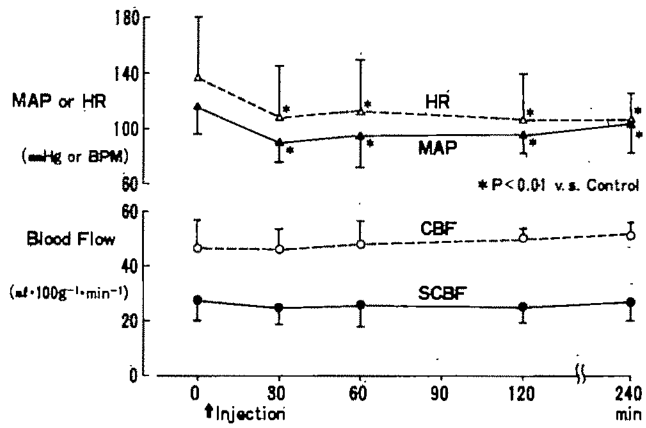

Figure 1. Time course of changes in spinal cord blood flow (SCBF), cerebral blood flow (CBF), mean arterial pressure (MAP), and heart rate (HR) after the subarachnoid administration of tetracaine (1 ml, 5 mg). Vertical bars indicate SD. Asterisk indicates that difference from control is statistically significant $P < 0.01$.

control animals for evaluation of the effects of acute blood loss alone on SCBF and CBF. Measurements of SCBF and CBF were made before and after the removal of 20% of estimated blood volume and again after reinfusion of the removed blood in these six animals.

Data are given as mean ± SD. The statistical significance of differences between groups was determined by analysis of variance for multiple comparisons followed by Student's *t*-test for paired data; $P < 0.05$ was considered to represent statistical significance.

Results

The subarachnoid administration of tetracaine, 5 mg in 1 ml of D7.5W, produced no significant change in either SCBF or CBF. Mean baseline values of SCBF and CBF were 27 ± 6 $ml\cdot 100\ g^{-1}\cdot min^{-1}$ and 47 ± 10 $ml\cdot 100\ g^{-1}\cdot min^{-1}$, respectively, during the following conditions: Pa_{O_2} 239 ± 65 mm Hg; Pa_{CO_2} 36.1 ± 3.0 mm Hg; pHa 7.39 ± 0.04; hemoglobin 14.4 ± 1.5 $g\cdot 100\ ml^{-1}$; serum K^+ and Na^+ were 3.6 ± 0.7 and 144.5 ± 6.0 mEq/L, respectively. Thirty minutes after tetracaine, SCBF and CBF, 25 ± 6 $ml\cdot 100\ g^{-1}\cdot min^{-1}$ and 46 ± 9 $ml\cdot 100\ g^{-1}\cdot min^{-1}$, respectively, remained stable for 240 min (Fig. 1). MAP and HR decreased significantly (117 ± 23 to 90 ± 25 mm Hg and 139 ± 40 to 110 ± 35 beats/min, respectively) and thereafter also remained stable for 240 min.

The subarachnoid administration of epinephrine alone, 100 µg, 300 µg, or 500 µg in 1 ml, caused variable changes in SCBF, but none of the changes were statistically significant (Table 1, Fig. 2). CBF remained stable after the subarachnoid epinephrine.

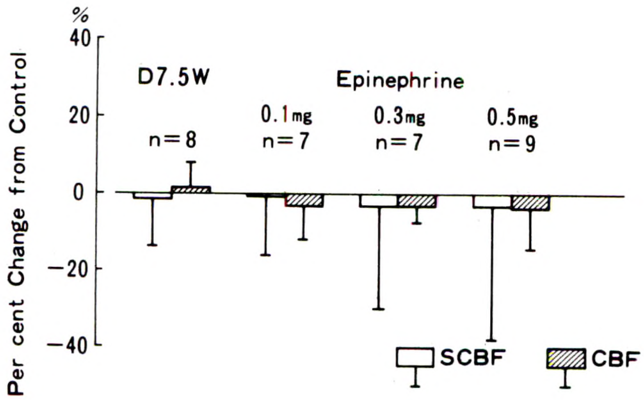

Figure 2. Percentage changes of spinal cord blood flow (SCBF) and cerebral blood flow (CBF) from control after the subarachnoid administration of epinephrine (1 ml; 0.1, 0.3, 0.5 mg) and 7.5% dextrose in water that had been used for dilution of drugs. (Data from our previous study (2).)

The responses of SCBF and CBF to hypercapnia were not affected significantly by subarachnoid tetracaine. Hypercapnia increased SCBF and CBF 27% and 35% before subarachnoid tetracaine, and 22% and 41% above baseline levels after subarachnoid tetracaine (Table 2). There was no statistically significant difference in these increases in either SCBF or CBF between before and after the subarachnoid tetracaine. CO_2 inhalation also increased CSFP significantly (Fig. 3) and decreased cerebral perfusion pressure (Table 2).

Acute blood loss (20% of the estimated blood volume of each dog) after subarachnoid tetracaine produced a statistically significant decrease (23 ± 16% of baseline) in SCBF (Table 3*A*), whereas in the absence of the subarachnoid tetracaine, SCBF did not change significantly (Table 3*B*). In both instances, CBF remained unchanged. MAP following acute blood loss decreased more in the presence of subarachnoid tetracaine than it did in the presence of halothane anesthesia alone (Table 3*A*,*B*); the MAP of 66 ± 8 mm Hg after acute blood loss in the former was significantly less than the 89 ± 16 mm Hg in the latter ($P < 0.05$).

Discussion

The subarachnoid administration of local anesthetics could affect local SCBF in six ways (2): 1) a direct action on the smooth muscles of vessels within the spinal cord; 2) a direct action on autonomic nerves innervating the arterial supply of the spinal cord; 3) a systemic action secondary to pharmacologically active plasma concentrations achieved after vascular absorption; 4) a direct supraspinal action on the vasomotor center after ascent of the local anesthetic through the CSF circulation into the ventricular system; 5) passive effects due to altered systemic hemodynamics secondary to spinal anesthesia; and 6) decreased metabolic demands of the spinal cord secondary to spinal anesthesia (8). In spite of these possibilities, our study failed to demonstrate any significant changes in SCBF after administration of 5 mg subarachnoid tetracaine in 1 ml of D7.5W. Our previous study has also demonstrated that subarachnoid lidocaine, 1 ml of 1, 2, 3, and 5% solution in 5 or 7.5% dextrose in water, had no significant effect on SCBF. In both studies, CBF was also measured simultaneously and found to remain unchanged.

Although quantitative differences can exist in the blood flow to the brain and spinal cord and in their metabolic responses (19,20), neither subarachnoid tetracaine nor lidocaine affects blood flow to either tissue. However, it can be speculated that our negative finding might be due to compensatory mechanisms involving the above six factors; the first two can be expected to increase local SCBF, and the last four probably decrease local SCBF. Since mechanisms controlling SCBF are thought to parallel those affecting CBF, the absence of measurable changes in CBF after the subarachnoid tetracaine could preclude the possibility that factors 3, 4, and 5 affected local SCBF in any important way. The results also may indicate that neither 1, 2, nor 6 is an important determinant affecting local SCBF, or perhaps that the effect on SCBF of factors 1 and 2 counteracts the effect of factor 6. In addition, since halothane increases CBF and decreases cerebral metabolic activity, it is possible that any effects of the subarachnoid tetracaine on SCBF might be minimized by halothane used as a basal anesthetic in the present study.

Porter et al. (6) demonstrated recently in cats anesthetized with pentobarbital that lidocaine 15 mg, tetracaine 5 mg, and mepivacaine 10 mg, administered subarachnoidally (all dissolved in 1 ml of D10W) produced no significant changes in SCBF or CBF as measured by the radioactive microsphere technique whereas when Kozody et al. (4,7) used radioactive microspheres to measure SCBF in dogs anesthetized with pentobarbital, lumbar subarachnoid tetracaine (20 mg) and lidocaine (100 mg) in 5 ml of physiologic saline produced significant increases in lumbar SCBF. In conscious rats, Crosby et al. (8) reported that spinal anesthesia with 0.75% of bupivacaine produces a statistically significant reduction (27–34%) in local SCBF measured by the iodo (^{14}C) antipyrine method. In dogs anesthetized with pentobarbital, bupivacaine decreases SCBF by 26–47% (5). Differences in the results of these studies might be due to differences in species and the methods used for measuring SCBF,

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Table 2. Effects of Hypercapnia on SCBF and CBF before and after the Subarachnoid Tetracaine in Dogs Anesthetized with Halothane (n = 7)

	Before spinal anesthesia		During spinal anesthesia	
	Control	Hypercapnia	Control	Hypercapnia
SCBF (ml·100 g^{-1}·min^{-1})	31.5 ± 8.1	39.9 ± 6.0[a]	26.8 ± 9.0	34.2 ± 13.6[a]
CBF (ml·100 g^{-1}·min^{-1})	51.1 ± 9.0	69.0 ± 18.0[a]	52.1 ± 10.8	73.6 ± 17.3[a]
HR (BPM)	94.3 ± 18.2	102.4 ± 17.7	87.9 ± 12.3	92.7 ± 19.7
MAP (mm Hg)	110.1 ± 12.4	109.4 ± 10.8	82.2 ± 11.4[b]	89.1 ± 7.6
CSFP (mm Hg)	7.5 ± 2.1	21.7 ± 3.6[a]	9.1 ± 0.4	21.2 ± 2.9[a]
PP (mm Hg)	102.0 ± 12.8	88.7 ± 13.3[a]	72.9 ± 11.2[b]	70.1 ± 9.3
Pa_{CO_2} (mm Hg)	36.7 ± 2.8	57.0 ± 7.8[a]	35.1 ± 2.6	56.7 ± 7.3[a]
Pa_{O_2} (mm Hg)	219 ± 11	158 ± 32[a]	217 ± 23	187 ± 46[a]
pHa	7.376 ± 0.004	7.205 ± 0.005[a]	7.400 ± 0.026	7.207 ± 0.005[a]
Hb (g/100 ml)	13.4 ± 1.8		13.0 ± 1.9	

Abbreviations: HR, heart rate; MAP, mean arterial pressure; CSFP, cerebrospinal fluid pressure; PP, cerebral or spinal cord perfusion pressure (MAP–CSFP) Hb, hemoglobin.
[a]$P < 0.01$ vs control for each of before and after spinal anesthesia.
[b]$P < 0.05$ vs control for before spinal anesthesia.

the metabolic demands of the cord, preexisting sympathetic tone of spinal cord vessels, characteristics of the local anesthetic agents employed, pH of the solution, the basal anesthetic used, or, especially, differences between blood flows in gray and white matter separately and in total blood flow.

It has been assumed that the addition of epinephrine to a local anesthetic for prolongation of spinal anesthesia reduces the vascular uptake of the local anesthetic because of subarachnoid vasoconstriction produced by the epinephrine. Although this mechanism of action has long been suspected, the data are conflicting. Kozody et al. (3) reported that in dogs epinephrine 200 μg significantly reduced lumbo-sacral dural blood flow but had no significant effects on local SCBF. But in a subsequent study, the same investigators found that in dogs anesthetized with pentobarbital, the addition of epinephrine (200 μg) to subarachnoid lidocaine (100 mg) prevented the increase in SCBF seen at 40 min with lidocaine alone (7), but epinephrine had no additive effect on the decrease in SCBF produced by subarachnoid bupivacaine (5). On the other hand, Porter et al. (6) found in cats anesthetized with pentobarbital that the addition of epinephrine (1:100,000) to lidocaine (15 mg), mepivacaine (10 mg), tetracaine (5 mg) in 10% dextrose solution had no effect on either SCBF or CBF. In the present study, we found that SCBF varied widely after subarachnoid epinephrine, 100, 300, and 500 μg dissolved in D7.5W, especially with higher concentration of the injection. The clinical implication of these conflicting studies is that epinephrine alone normally affects local SCBF only minimally, but in the presence of abnormally increased SCBF, it decreases SCBF.

Intracranial and, possibly, spinal arteries are remarkably unresponsive to vasoconstrictors; large intracranial arteries, for example, are 30–50 times less sensitive to norepinephrine than are extracranial arteries of similar size (21). Crawford et al. (22), using the "pial window" technique, reported that microapplication of norepinephrine to spinal pial vessels results in vasoconstriction averaging 28.8 ± 5.1%. Since an equimolar concentration of an alpha-adrenergic blocker such as phentolamine prevented this response, it appears that vasoconstriction is mediated via alpha-adrenergic receptors. This concept seems to agree with the results of our previous study in which phenylephrine in the lumbar subarachnoid space caused a significant reduction in SCBF in a dose-related fashion (2). On the other hand, Crosby and Szabo (23) have reported that in conscious animals, subarachnoid norepinephrine (5 μg) slightly increases SCBF in the gray matter, probably by stimulating the spinal cord metabolism (24).

Along with differences in vasoconstrictive agents, as well as different rates of blood flow in gray and white matter of the cord, basal anesthetics used in in vivo animal studies could also influence the effects of subarachnoid vasoconstrictors on SCBF. It is also known that the pH of the extracellular fluid of the brain, and probably the spinal cord as well, have a major influence on controlling vascular tone in the smooth muscle of small arteries and arterioles in the brain (25,26). Because of the low pH of the epinephrine solution used in the present study, a possible vasoconstricting action of a large dose of epinephrine on the spinal cord vessels might be counteracted with vasodilation due to the low pH of the solutions. Thus, further studies are needed before a pharmacological conclusion can be reached concerning the effect of

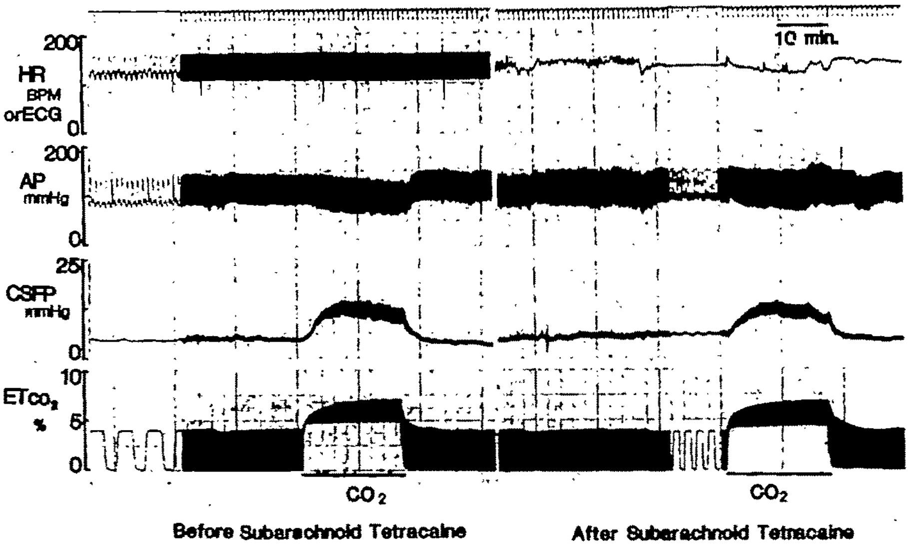

Figure 3. Polygraph tracings of heart rate (HR), arterial pressure (AP), cerebrospinal fluid pressure (CSFP), and end-tidal carbon dioxide concentration (ET_{CO_2}) during CO_2 inhalation before (left) and after (right) spinal anesthesia.

subarachnoid epinephrine on local blood flow of the spinal cord. The gray and white matter of the cord have different rates of blood flow (16) and thus may respond differently to the drug.

SCBF has an autoregulatory capacity the range of which has been reported to be 60–150 mm Hg (14) and 50–135 mm Hg (15). Since the alpha-blocker phenoxybenzamine impairs the autoregulation (27) but the beta-blocker propranolol (28) does not, it appears that the alpha-adrenergic nervous system plays an important role in the spinal cord vascular autoregulation. Neither transection of spinal cord (29) nor blockade of peripheral ganglia impairs the autoregulation (30). Previous studies by us (2) and by Porter et al. (6) also suggest that spinal anesthesia maintains autoregulation of SCBF. The results of the present study, however, indicate that acute hypotension (MAP 66 ± 8 mm Hg) due to blood loss during spinal anesthesia with tetracaine caused a significant reduction (about 23%) in SCBF without affecting CBF, whereas in the absence of subarachnoid tetracaine, acute blood loss affected neither SCBF nor CBF in dogs anesthetized with halothane. These results may exclude the possibility that halothane anesthesia per se (31) influences the present results in any important way, although acute blood loss decreased MAP more in the presence of spinal anesthesia than without it. Thus, it is likely that the decrease in SCBF is related to an alteration of autoregulation of SCBF by spinal anesthesia with tetracaine.

On the other hand, local SCBF responses to hypercapnia were not affected by subarachnoid tetracaine. Previous investigations established a relationship between SCBF and Pa_{CO_2} in which SCBF increased 0.2–1.2 ml·100 g^{-1}·min^{-1} per mm Hg change of Pa_{CO_2} (32). Scremin and Decima (16) also reported a significant difference in blood flow responses to CO_2 in gray and white matter of the spinal cord. The relatively less reactivity of SCBF to CO_2 in the present study (8.4 ml·100 g^{-1}·min^{-1} increase in SCBF for a 20 mm Hg increase of Pa_{CO_2} before spinal anesthesia, and 7.4 ml·100 g^{-1}·min^{-1} increase in SCBF for a 22 mm Hg increase of Pa_{CO_2} after spinal anesthesia, Table 2) might be due not only to measuring the blood flow in the white matter, but also might be related to a decrease in perfusion pressure because of the increase in CSFP (33). The mechanism by which arterial hypercapnia increases SCBF is probably the same as that for CBF, that is, changes in Pa_{CO_2} are quickly reflected in the P_{CO_2} of the cerebrospinal fluid (CSF) and thus produce an increase in SCBF due to dilation of arterial smooth muscles of the spinal cord. Halothane anesthesia has little effect on the responsiveness of CBF to changes in Pa_{CO_2} (31,34), and this probably also applies to SCBF as well, though there is a report suggesting that CO_2 responses are faster in vessels of the spinal cord than in those of the brain (35). Because the vascular tone of the cord vessels may be diminished in the presence of spinal anesthesia, and CO_2 responsiveness of CBF has been reported to be abolished in the presence of a vascular smooth muscle dilator (nitroprusside) or ganglionic blockade (trimethaphan) in dogs anesthetized with halothane and nitrous oxide (36), we speculate that local SCBF during hypercapnia could decrease after the subarachnoid tetracaine, probably by distribution of blood flow away from the local spinal cord, i.e., a steal phenomenon. However, we observed almost the same increase in local SCBF before and after subarachnoid tetracaine, though the perfusion pressure

Table 3. Effects of Acute Blood Loss on SCBF and CBF during Halothane Anesthesia with (A) or without (B) Spinal Anesthesia (Tetracaine)

	SCBF (ml·100 g^{-1}·min^{-1})	CBF (ml·100 g^{-1}·min^{-1})	MAP (mm Hg)	HR (beats/min)	Hb (g/100 ml^{-1})	Pa_{CO_2} (mm Hg)
A (n = 5):						
Control	30.4 ± 16.6	50.9 ± 3.4	97 ± 7	123 ± 33	13.8 ± 1.6	34.4 ± 4.2
Spinal tetracaine	30.6 ± 14.6	49.7 ± 4.8	87 ± 13	115 ± 18	13.3 ± 2.3	34.2 ± 1.9
Blood loss (20% of EBV)	24.1 ± 14.6[a]	49.4 ± 6.7	66 ± 8[a]	145 ± 36[a]	9.6 ± 2.1[a]	33.3 ± 3.1
B (n = 6):						
Control	27.9 ± 6.3	47.3 ± 10.9	110 ± 14	137 ± 16	13.2 ± 1.3	35.2 ± 3.1
Blood loss (20% of EBV)	26.7 ± 6.7	43.2 ± 11.4	89 ± 16[b]	161 ± 18[b]	10.4 ± 1.5[b]	34.0 ± 2.8
Reinfusion	29.9 ± 4.2	45.7 ± 10.9	124 ± 6	131 ± 17	12.6 ± 1.0	33.7 ± 1.5

Abbreviations: SCBF, spinal cord blood loss; CBF, cerebral blood flow; MAP, mean arterial pressure; HR, heart rate; Hb, hemoglobin.
[a]$P < 0.05$ vs control and spinal tetracaine.
[b]$P < 0.05$ vs control and reinfusion.
Each number indicates mean ± SD.

during hypercapnia decreased more after spinal anesthesia. The results agree with the finding that the response of lumbar SCBF to changes in Pa_{CO_2} is not affected by a low thoracic cordotomy (16). Because hypercapnia does not seem to change the energy state of the brain (37) and spinal anesthesia could decrease spinal metabolism as reported with bupivacaine in conscious animals (8), it is unclear whether preservation of the CO_2 reactivity of SCBF during spinal anesthesia with tetracaine can be considered to be necessarily beneficial. At present, because we examined changes in SCBF only at two levels of Pa_{CO_2}, we tentatively conclude that spinal anesthesia leaves the local reactivity of SCBF to respiratory acidosis unchanged.

Our data demonstrate two aspects that may be important with regard to the relative lack of information concerning the effects of spinally administered agents on the spinal cord circulation. First, normal spinal cord blood flow is not affected by subarachnoid tetracaine and epinephrine. This supports the observation that there are no case reports of spinal cord ischemia after spinal anesthesia either in normal subjects or in patients with chronic spinal cord pathology. Second, during spinal anesthesia, the autoregulatory capacity of the spinal cord circulation to hypotension is altered, to some extent, but the blood flow responses to hypercapnia remain intact. The excellent safety record of modern spinal anesthesia suggests that any changes in the autoregulation of SCBF are small and well tolerated, but it may be prudent, in patients with altered homeostatic mechanisms, to avoid profound hypotension or hypercapnia during spinal anesthesia.

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β-Blockade Reverses Regional Dysfunction in Ischemic Myocardium

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LEONE BJ, LEHOT J-J, FRANCIS CM, CUTFIELD GR, FOËX P. β-Blockade reverses regional dysfunction in ischemic myocardium. Anesth Analg 1987;66:607–14.

To determine the protective effect of oxprenolol-induced β-blockade on the compromised myocardium (critical constriction of the left anterior descending coronary artery) against the adverse effect of high concentrations of halothane, halothane dose–response curves were obtained in six dogs in each of three phases: preconstriction (control), critical constriction, and critical constriction with the addition of 0.3 mg/kg intravenous oxprenolol. The extent of depression of ventricular function was essentially the same in the three phases. However, at high halothane concentrations (2.0% inspired), the depression of systolic shortening in the compromised segment was significantly minimized after oxprenolol so that shortening was 10.2% ± 1.8 instead of 6.5% ± 1.4 ($P < 0.05$); moreover the large increase in postsystolic shortening observed during critical constriction was abolished after oxprenolol. This suggests a protective effect of oxprenolol on regional myocardial function in the presence of critical constriction, possibly by an effect on myocardial metabolism or endocardial blood flow.

Key Words: HEART, MYOCARDIAL FUNCTION—β-blockade.

Beta-blockade in acute myocardial ischemia has been shown to improve global myocardial performance by decreasing the hemodynamic dysfunction associated with ischemia (1,2). This effect has been variously attributed to a decreased oxygen demand by reducing the chronotropic and inotropic state of the myocardium, an increased oxygen supply by endocardial redistribution of blood flow, or both (1–3). These studies of the effects of β-blockade have employed ligation of a coronary artery, analogous to an acute infarction, as the cause of ischemia rather than a narrowed or critically constricted coronary artery, which supplies adequate coronary flow for basal function but is incapable of increasing flow to match increased demand and has lost the capacity of autoregulation. Also, much of this work has dealt with global hemodynamics, electrocardiographic changes; and diminution of infarct size (1,2) rather than regional wall function.

Regional dysfunction, in the form of shortening of a myocardial segment after the cessation of systole (PSS), has been shown to occur in ischemic myocardium without concurrent global dysfunction (4). Halogenated anesthetics at high concentrations exacerbate this dysfunction in ischemic areas (4,5). A recent study has suggested improvement of regional function in ischemic myocardial segments when subjected to β-blockade (6). We therefore decided to employ a critical constriction model of coronary ischemia to determine whether β-blockade reverses regional myocardial dysfunction caused by halothane.

Materials and Methods

Studies were performed on six mongrel dogs weighing between 18 and 33 kg. The dogs were premedicated with intramuscular morphine sulfate (0.3 mg/kg). Anesthesia was induced with thiopental (15 mg/kg) and the trachea intubated. Constant-volume intermittent positive pressure ventilation was begun at a rate of 12 breaths/min with a mixture of 30% oxygen and 70% nitrogen to which sufficient carbon dioxide was added to maintain end-tidal carbon dioxide concentration at 5.3%. Anesthesia was maintained during preparation with 1.0–1.5% inspired halothane supplied by a Fluotec Mark III vaporizer (Fraser/Sweatman

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Glossary of Abbreviations Used

SAP	Systolic arterial pressure
DAP	Diastolic arterial pressure
MAP	Mean arterial pressure, calculated by the following formula: [2(DAP) + SAP]/3
LVEDP	Left ventricular end-diastolic pressure
LV dP/dt	The first derivative of left ventricular pressure. LV dP/dt_{max} refers to the maximum positive value of LV dP/dt
LAD	Of or pertaining to the left anterior descending coronary artery
LC	Of or pertaining to the left circumflex coronary artery
EDL	End-diastolic length of a myocardial segment, expressed in millimeters
ESL	End-systolic length of a myocardial segment, expressed in millimeters
$L_{min}d$	Minimum length of a myocardial segment attained during diastole, expressed in millimeters
SS	Systolic shortening of a myocardial segment, expressed as a percentage of EDL, calculated by the following formula: $[(EDL - ESL)/EDL] \times 100$
PSS	Postsystolic shortening of a myocardial segment, expressed as a percentage of the total segment shortening, calculated by the following formula: $[(ESL - L_{min}d)/(EDL - L_{min}d)] \times 100$

Inc.), the calibration of which was checked by a Riken refractometer. Temperature was measured via a thermistor probe in the midesophagus and was maintained between 36°C and 37°C by a heating element incorporated into the operating table. An intravenous cannula was then placed in the inferior vena cava via the femoral vein and used to infuse 0.9% saline at a rate of 4 $ml \cdot kg^{-1}h^{-1}$. The left carotid artery was exposed and a rigid 8-French (2.76 mm outside diameter) polyethylene catheter was inserted to within 1 cm of the aortic valve for systemic pressure measurement by a Statham pressure transducer. This arterial cannula was also used to withdraw arterial blood samples.

A left thoracotomy was then performed, and the fifth and sixth ribs removed. The heart was exposed and suspended in a pericardial cradle. The fat pad was dissected from the aortic root and an appropriately sized electromagnetic flow probe (SEM 230 SE Laboratories) was placed around the aortic root. A left ventricular catheter was inserted via a stab wound in the apical dimple and connected to a Statham pressure transducer. A flexible polyvinyl catheter was inserted into the pulmonary artery via the right ventricular outflow tract.

The left anterior descending coronary artery (LAD) was dissected free distal to the second diagonal branch. A 3-0 woven Dacron suture was placed loosely about the artery and connected to a micrometer-controlled spring-suspended snare that could be tightened or loosened in increments of 0.025 mm. An electromagnetic flow transducer (SEM 230 SE Laboratories) of appropriate diameter was then placed around the vessel proximal to the snare. A second 3-0 woven Dacron suture, placed distal to the flow probe, served as a device for intermittent occlusion to verify loss of coronary hyperemic response as evidence of critical constriction.

Regional myocardial function was assessed by sonomicrometry (7–9). One pair of piezoelectric crystals was placed at the subendocardium, in the region supplied by the distal LAD, while the other pair was located in a region corresponding to the flow distribution of the left coronary artery (LC). These crystals serve as emitter–receiver pairs utilizing ultrasonic transit times through the myocardium to determine the instantaneous distance between the crystals. A continuous analog signal of dynamic segment length is provided by a repetitive stimulation rate of 1 kHz.

The signals were recorded on a Mingograf 81 eight-channel recorder (Elema Schonander, Stockholm, Solna, Sweden). Aortic and left ventricular pressures were recorded, as were aortic flow and left ventricular (LV) dP/dt.

Systole was defined as beginning at the upward (positive) deflection of the LV dP/dt signal and ending when aortic flow ceased. Segment length data were measured with the end points of systole as reference points. Abnormal contractile function patterns were recorded when ischemia was present in the region where the crystals were implanted. These patterns consisted of myocardial shortening in early diastole after aortic valve closure, known as PSS. Systolic lengthening was not seen, although this has been described with ischemia (10).

Protocol

The purpose of the study was to determine whether β-blockade reversed the regional dysfunction caused by high concentrations of halothane in the presence of critical constriction of the LAD. Greater depression of regional contractile performance and the appearance of regional dysfunction has been demonstrated when halothane dosage is increased in the presence of critical LAD constriction (4). We duplicated this experimental protocol, utilizing a control phase and a critically constricted phase, and then administered 0.3 mg/kg intravenous oxprenolol to determine whether β-blockade reversed the halothane-induced changes

in regional function of ischemic myocardium. To this end, dose–response curves to halothane were obtained before and after critical constriction of the LAD, and a further dose–response curve was obtained after β-adrenoceptor blockade while critical constriction was maintained.

At the conclusion of surgical preparation, the halothane-inspired concentration was adjusted to 0.8% and the preparation allowed to stabilize for 1 hr. During this stabilization period, instruments were recalibrated, arterial blood-gas tensions were analyzed, ventilation was adjusted to normocarbia, and small volumes of dextran were given to correct any hypovolemia. Sodium bicarbonate was given when appropriate. Each dog then underwent a dose–response curve to halothane in each of three phases. Phase 1 was a control phase, in which no other intervention was made, and a four-point halothane dose–response curve (0.7%, 1.0%, 1.5%, 2.0%, corresponding to stage I, stage II, stage III, and stage IV, respectively) was obtained with a 20-min interval after changing the inspired halothane concentration to ensure achievement of a steady-state end-tidal concentration. These inspired halothane concentrations were used to produce four levels of halothane-induced cardiovascular depression.

A pilot study was done to examine the relationship between inspired and end-tidal halothane concentrations utilizing a Riken refractometer (11). The samples were confirmed as being end tidal by comparing the carbon dioxide tension of the sample with that obtained by continuous analysis with the infrared analyzer. The values agreed to within 0.1%. The results showed that the end-tidal halothane concentration reached a steady-state plateau 7 min after a change in inspired concentration. These plateau concentrations were linearly related, so that as the inspired halothane concentration was increased from 0.5% to 2.0% in steps of 0.5%, a proportionate stepwise increase occurred in the end-tidal halothane concentration from 0.36% ± 0.05 to 1.64% ± 0.05. No deviations in the end-tidal concentration from steady state were noted from the achievement of the plateau phase (at 7 min) to subsequent hemodynamic measurements (at 20 min).

Phase 2 involved the application of a critical constriction to the LAD using the micrometer snare and performing an identical four-point halothane dose–response curve, producing equivalent levels of cardiovascular depression. Critical constriction was obtained by 1.25 mm incremental tightening of the LAD snare until an obvious decrease in the pulsatile pattern of the coronary flow tracing occurred. The snare was tightened further in increments of 0.63 mm until the first changes indicative of dysfunction occurred (PSS). The snare was then loosened slightly until these changes resolved. The critical nature of the constriction was confirmed by demonstration that a 10-sec total occlusion of the LAD produced no postocclusion hyperemic response.

In phase 3, critical constriction was maintained and the β-blocker oxprenolol (0.3 mg/kg) was given. A third halothane dose–response curve, utilizing the same concentrations of halothane as the previous two phases and achieving equivalent levels of cardiovascular depression, was then performed, beginning 20 min after the administration of oxprenolol.

Computation

The data were manually digitized and analyzed on a Hewlett-Packard 9825A calculator.

Results were analyzed for statistical significance using analysis of variance and Duncan's test, with $P < 0.05$ considered to be significant.

Results

Table 1 displays the global hemodynamic data obtained with each phase and Table 2 shows the regional function for the two segments studied.

Global Hemodynamics (see Table 1)

Phase 1. The control phase shows dose-dependent depression of systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), LV dP/dt_{max}, and coronary perfusion pressure as the halothane concentration increased. At higher halothane concentrations (stages III and IV), heart rate was significantly decreased.

Phase 2. With the application of critical constriction in phase 2, halothane again caused significant depression of SAP, DAP, MAP, and LV dP/dt_{max}. No difference in heart rate was observed. No significant differences were noted between the values in phase 1 and phase 2, with the exception of LV dP/dt_{max}, SAP, and MAP, which were significantly lower at stage I in the presence of critical constriction.

Phase 3. The addition of oxprenolol in phase 3 caused no alteration in the dose-dependent myocardial depression due to halothane. However, in the presence of critical constriction, LV dP/dt_{max} was generally higher after oxprenolol (phase 3) than before its administration (phase 2). This became statistically significant for LV dP/dt_{max} in stage III. Heart rate was

Table 1. Global Hemodynamics (Mean ± SEM)

	Phase 1 (preconstriction)			
Stages	I	II	III	IV
Heart rate (beats/min)	108.7 ± 8.9	101.7 ± 8.2	96.5[a] ± 8.2	90.8[a] ± 8.8
Systolic arterial pressure (mm Hg)	103.2 ± 4.3	89.5[a] ± 6.0	74.8[a] ± 6.4	57.3[a] ± 5.6
Diastolic arterial pressure (mm Hg)	77.2 ± 5.5	60.7[a] ± 6.5	48.7[a] ± 6.9	36.3[a] ± 5.0
Mean arterial pressure (mm Hg)	82.0 ± 4.7	71.0[a] ± 6.1	57.2[a] ± 6.7	43.3[a] ± 5.2
Left ventricular end diastolic pressure (mm Hg)	5.0 ± 0.5	5.8 ± 0.5	7.2 ± 0.8	6.5 ± 0.8
LV dP/dt_{max} (mm Hg/sec)	1433 ± 117	1083[a] ± 60	750[a] ± 43	550[a] ± 76
Coronary perfusion pressure (mm Hg)	78.2 ± 5.6	54.8[a] ± 6.6	41.5[a] ± 6.5	29.8[a] ± 4.7

[a] $P < 0.05$ versus stage I of same condition.
[b] $P < 0.05$ versus same stage of phase 1 (preconstriction).
[c] $P < 0.05$ versus same stage of phase 2 (critical constriction).

Table 2. Regional Function (Mean ± SEM)

	Phase 1 (preconstriction)			
Stages	I	II	III	IV
LAD segment				
End diastolic length (mm)	10.5 ± 0.3	10.4 ± 0.3	10.5 ± 0.4	10.6 ± 0.4
Systolic shortening (%)	20.2 ± 2.1	16.5[a] ± 1.9	14.5[a] ± 1.8	10.8[a] ± 1.6
Postsystolic shortening (%)	0 ± 0	0 ± 0	0 ± 0	11.0[a] ± 6.0
LC segment				
End diastolic length (mm)	9.8 ± 0.9	9.9 ± 0.8	10.0[a] ± 0.9	10.2[a] ± 0.9
Systolic shortening (%)	15.5 ± 1.4	13.5 ± 1.5	10.7[a] ± 0.8	8.8[a] ± 0.8
Postsystolic shortening (%)	1.0 ± 1.0	4.0 ± 3.0	15.0[a] ± 7.0	15.0[a] ± 5.0

[a] $P < 0.05$ versus stage I of same condition.
[b] $P < 0.05$ versus same stage of phase 1 (preconstriction).
[c] $P < 0.05$ versus same stage of phase 2 (critical constriction).

significantly reduced at high halothane concentration (stage IV). Coronary perfusion pressure was not influenced by oxprenolol.

Note that at stages III and IV the mean differences in DAP were less than 2.0 mm Hg and 1.3 mm Hg, respectively. No significant change in LV and diastolic length (EDP) was observed at any stage in all three phases. There were no differences in heart rate between phases at the higher halothane concentrations (stages III and IV).

Regional Function (see Table 2)

Phase 1. The regional function in the LAD region declined with increasing halothane concentration, reflected in the decrease by about 10% in SS. A small but significant amount of PSS (11 ± 6%) was apparent with an inspired halothane concentration of 2.0% (stage IV).

The LC region showed depression of myocardial function similar to that observed in the LAD region. The EDL increased slightly, being statistically significant in stages III and IV. SS declined, also achieving significance in stages III and IV, and some PSS developed.

Phase 2. The application of critical constriction caused changes in myocardial function in the region supplied by the LAD. Although no difference was noted in EDL, SS was substantially reduced (20% ± 1 to 16.3% ± 1.3, $P < 0.05$), and PSS was significantly greater (29% ± 9 vs 11% ± 6) than in phase 1 at stage IV. This agrees with previous work showing greater depression of myocardial regional function accompanied by dysfunction in areas of ischemia when volatile anesthetics are used (5,10).

The LC region showed improvement in function at stage IV, when PSS was significantly lower when compared with phase 1. SS was slightly greater at stage IV than before the application of critical constriction to the LAD artery, but this did not reach statistical significance.

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Phase 2 (critical constriction)				Phase 3 (critical constriction with oxprenolol)			
I	II	III	IV	I	II	III	IV
99.5 ± 11.7	94.0 ± 9.1	93.5 ± 9.9	95.8 ± 10.5	101.2 ± 8.4	98.0 ± 8.0	92.3 ± 8.4	88.2[a] ± 10.1
93.3[b] ± 6.0	83.5[a] ± 5.2	71.2[a] ± 5.4	52.2[a] ± 8.3	93.7[b] ± 5.1	82.2[a] ± 5.0	74.0[a] ± 6.3	57.0[a] ± 8.2
72.0 ± 9.3	56.7[a] ± 4.8	47.0[a] ± 5.2	35.0[a] ± 6.1	61.8[b,c] ± 6.1	53.2[a] ± 4.8	46.7[a] ± 5.6	36.0[a] ± 6.1
74.5[b] ± 6.7	66.0[a] ± 4.9	54.8[a] ± 5.3	41.2[a] ± 6.6	72.5[b] ± 5.6	62.8[a] ± 4.7	57.3[a] ± 5.1	43.2[a] ± 6.8
5.7 ± 0.8	5.8 ± 1.0	6.3 ± 1.0	7.2 ± 0.8	5.8 ± 0.8	5.5 ± 0.7	6.5 ± 0.9	7.2 ± 0.8
1133[b] ± 61	983[a] ± 47	733[a] ± 49	483[a] ± 83	1317 ± 147	1083[a] ± 135	817[a,c] ± 95	575[a] ± 85
72.0 ± 9.0	55.2[a] ± 6.2	45.7[a] ± 6.5	32.0[a] ± 6.5	56.0[b,c] ± 6.2	47.7 ± 5.1	40.2[a] ± 5.6	28.8[a] ± 6.2

Phase 2 (critical constriction)				Phase 3 (critical constriction with oxprenolol)			
I	II	III	IV	I	II	III	IV
10.4 ± 0.3	10.4 ± 0.3	10.5 ± 0.4	10.6 ± 0.6	10.3 ± 0.4	10.3 ± 0.4	10.6 ± 0.4	10.6 ± 0.4
16.3[b] ± 1.3	17.2 ± 2.0	13.2 ± 1.7	6.5[a,b] ± 1.4	17.5 ± 2.1	16.3 ± 2.0	13.5[a] ± 2.1	10.2[a,c] ± 1.8
0 ± 0	0 ± 0	12.0[a] ± 7.0	29.0[a,b] ± 9.0	3.0 ± 3.0	0 ± 0	7.0 ± 7.0	10.0[a,c] ± 7.0
9.9 ± 0.9	10.0 ± 0.9	10.1 ± 0.9	10.2[a] ± 0.9	9.7[c] ± 0.9	9.7 ± 0.8	9.9 ± 0.8	10.1[a] ± 0.8
14.0 ± 1.3	12.8 ± 0.8	9.2[a] ± 1.0	10.3[a] ± 1.0	15.3 ± 1.3	14.5 ± 1.1	14.0[c] ± 1.2	11.5[a] ± 1.6
2.0 ± 2.0	4.0 ± 2.0	18.0[a] ± 6.0	6.0 ± 4.0	3.0 ± 2.0	3.0 ± 2.0	5.0[b,c] ± 3.0	4.0[b] ± 3.0

Phase 3. Administration of the β-blocker oxprenolol improved regional function of the ischemic LAD segments. This was most strikingly demonstrated in the significant decrease in PSS seen in stage IV. Oxprenolol reduced PSS in stage IV to the extent that it was no different from phase 1, that is, from the normal, nonischemic value. SS was significantly higher in stage IV than in the same stage with constriction alone. With oxprenolol and critical constriction, SS was not different from the control phase.

In the LC segment, SS did show a trend toward improvement in function from phase 2 that was significant in stage III. However, the PSS did not change from the constricted values.

Discussion

The administration of β-blockers has a protective effect on the left ventricle during ischemia. Libby et al. (2), using a coronary ligation model in dogs, demonstrated that the administration of practolol improved ischemia-induced ST-segment elevations. This was deemed a protective effect and postulated to be the result of decreased myocardial oxygen demand as a consequence of a practolol-induced diminished inotropic state. Mueller et al. (1) studied 20 patients with acute myocardial infarction and found that treatment with propranolol improved myocardial oxygenation. Although a decreased coronary blood flow was noted after propranolol, myocardial oxygen demand was thought to diminish more, and thus the myocardial oxygen balance to improve, or even normalize.

We chose intravenous oxprenolol, a nonspecific β antagonist, to establish β-blockade. Oxprenolol is equipotent to propranolol in blocking β receptors, and their onsets of action similar (less than 10 min) with

Table 3. Comparison of Coronary Perfusion Pressures and Percent PSS

Dog	Percent PSS	CPP (mm Hg)
1	0	26
2	22	44
3	33	41
4	0	17
5	0	33
6	13	18

Values of percent PSS and corresponding coronary perfusion pressure (CPP) for six dogs during phase 1 (preconstriction) at stage IV (halothane 2.0%). Note that no dog achieves a CPP value distinctly lower than 18.5 mm Hg ± 1.7, shown to be the zero flow pressure by Verrier et al. (13).

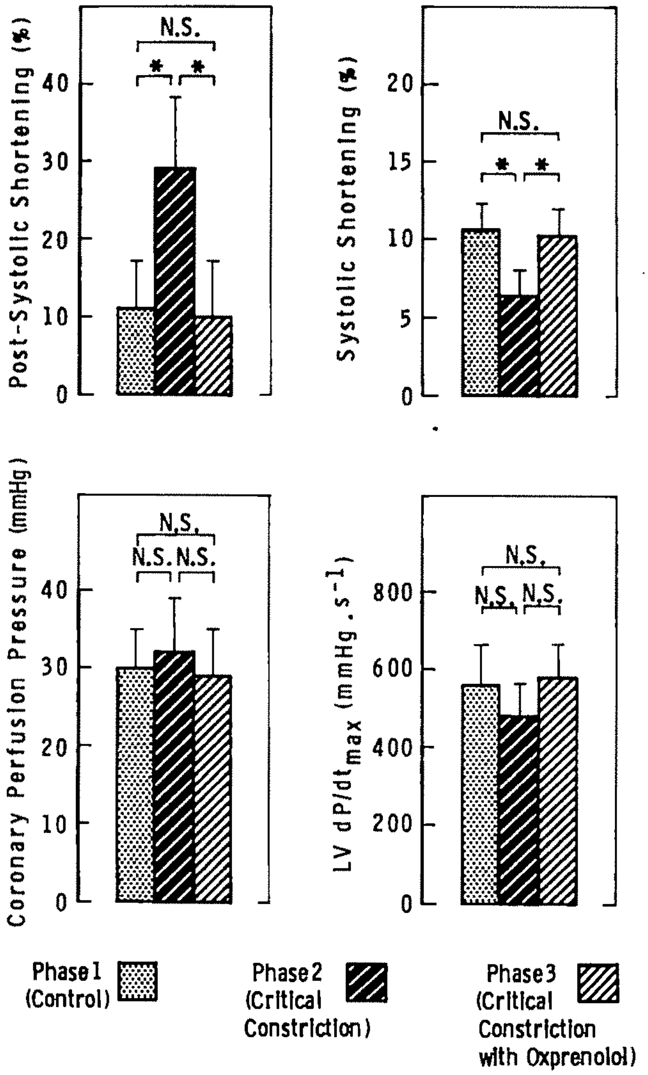

Figure 1. The application of critical constriction during stage IV (high halothane concentration) caused significant dysfunction in the LAD (ischemic) region, as evidenced by changes in systolic shortening (decrease) and postsystolic shortening (increase). No differences were noted in global hemodynamics or left ventricular performance, represented by coronary perfusion pressure and LV dP/dt$_{max}$. Administration of oxprenolol reversed the regional dysfunction in the LAD segment seen with critical constriction while not affecting global hemodynamics or left ventricular inotropy. Note that all of these values are significantly different from stage I values during the same experimental phase, reflecting halothane dose-dependent myocardial depression (see also Tables 1 and 2).

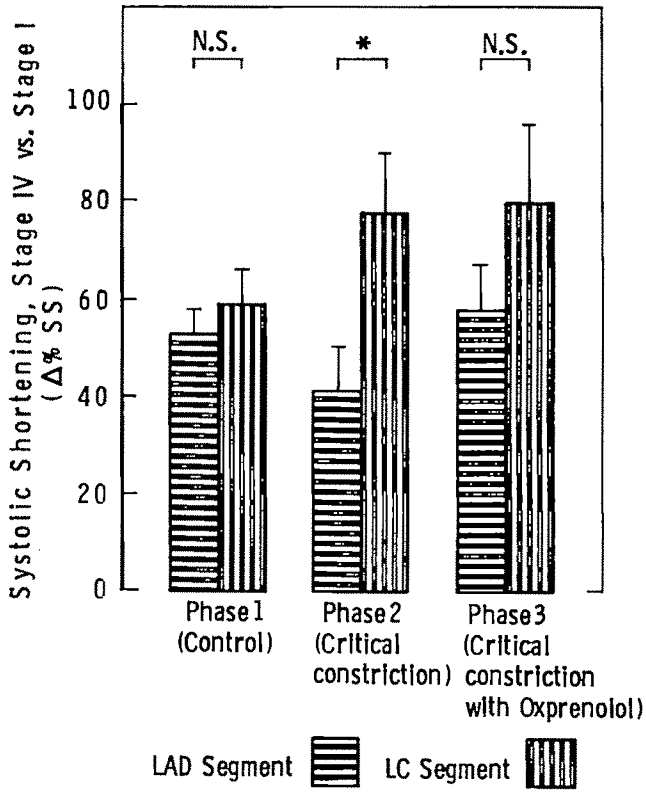

Figure 2. The differences in the contractile performance (represented by a change in systolic shortening from stage I) of the LAD (ischemic) and the LC (nonischemic) segments during stage IV of each experimental phase. The application of critical constriction causes a difference between LAD and LC systolic shortening, reflecting more depression of the LAD segment and improvement in the LC segment. Administration of oxprenolol during critical constriction abolishes this difference by improving LAD contractile function.

intravenous administration (12). Oxprenolol has slight intrinsic sympathomimetic activity (ISA) (13–15), and this ISA results in oxprenolol causing no significant decrease in cardiac performance or global hemodynamics (16). The dosage of oxprenolol employed (0.3 mg/kg) has been shown to cause an eightfold shift of the midpoint of the isoprenaline dose–response curve (17), resembling a clinically effective degree of β-blockade. Since oxprenolol administration results in β-blockade without significant hemodynamic depression, any differences in myocardial function are due to direct effects of β-blockade on regional myocardial oxygen demand or supply rather than the effects of global reduction in oxygen demand from global hemodynamic depression.

As observed previously, a substantial amount of PSS was observed in myocardium supplied by a critically constricted artery at high halothane concentrations (6). Surprisingly, however, some PSS occurred at stage IV (inspired halothane concentration 2.0%) prior to critical constriction (11% vs 0% at stages I, II, and III, $P < 0.05$). PSS has been thought to be a purely ischemic phenomenon that did not occur in myocardium with a normal blood supply. Although ischemia due to profound cardiovascular depression with subsequent inadequate coronary perfusion pressure is plausible, three dogs developed PSS in stage IV of phase 1 despite having CPP equal to or greater than 18.5 ± 1.7 mm Hg (see Table 3), a value Verrier et

al. have shown supplies adequate flow to the dog heart during halothane anesthesia (18). Thus the appearance of a small amount of PSS prior to critical constriction at 2.0% inspired halothane may represent an effect of halothane on regional function rather than ischemia.

In phase 2, critical constriction was applied to the LAD. The application of critical constriction results in the loss of local autoregulation of coronary blood flow to the area distal to the constriction (19). Therefore, the blood supply to this region is pressure dependent and must decrease sharply with increasing halothane concentrations. In this setting, the development of PSS suggests ischemia in the myocardium supplied by the critically constricted LAD. Previous studies on the effect of halothane on coronary blood flow in a critically narrowed coronary artery have shown that flow is sharply reduced when the inspired halothane concentration exceeds 1.5% (10). Although a flow probe was placed on the LAD, it was used only to verify the critical nature of the constriction. To measure coronary flow accurately throughout the study, multiple occlusions to define zero flow would have been required and by their repetition might have caused some ischemic damage and thus obscured the protective effect of β-blockade.

Regional function, in the form of SS, was significantly more depressed in the LAD segment during phase 2 (critical constriction of the LAD) as compared with the phase 1 (control). PSS in the LAD region increased with critical constriction, indicating greater regional dysfunction than before constriction. These results agree with previous results utilizing a similar model of myocardial ischemia (4,10). Oxprenolol (phase 3) significantly reduced regional dysfunction (PSS) (29% $\pm$ 9 to 10% $\pm$ 7, $P < 0.05$, Fig. 1) and significantly increased regional contractile performance (SS) (6.5% $\pm$ 1.4 to 10.2 $\pm$ 1.8, $P < 0.05$, Fig. 1) to values essentially identical to those during phase 1 (control, i.e., prior to critical constriction) with high halothane. Thus the administration of oxprenolol significantly improved the contractile performance of an ischemic region of myocardium during high halothane concentration, reversing the deleterious effect of critical coronary artery stenosis on regional myocardial function.

Oxprenolol caused no significant changes in global ventricular function or heart rate. Improvement of regional function occurred at stage IV, when the reduction in PSS and increase in SS with oxprenolol (phase 3) occurred. At this stage, coronary perfusion pressure was slightly reduced by comparison with phase 2 and LV dP/dt_{max} slightly increased (Fig. 1). This lack of depression of global LV contractile function by oxprenolol suggests that its protective effect under the conditions of this study is not mediated by a decrease in inotropic state of the myocardium, relative to coronary blood flow, as has been theorized (6). Because the coronary perfusion pressure was slightly lower after oxprenolol, there was insufficient time for the development of collateral blood supply, and all capacity for dilation of the local vasculature was abolished by the application of critical constriction (19), improvement in total blood flow to the ischemic region is unlikely. It may be that oxprenolol improves the efficiency of myocardial oxygen utilization, a mechanism that has been suggested for other β-blockers (1–3). Redistribution of blood flow from the epicardium to the endocardium, which occurs during infarction with propranolol (20), may also occur with oxprenolol during ischemia. Thus, either a redistribution of the limited regional blood flow or improved myocardial oxygen utilization may be the mechanism by which oxprenolol improved the function of an ischemic region of myocardium.

Differences between LC and LAD function during LAD ischemia have been commented on recently (21). In the model of ischemia used by Lew and colleagues, the LAD was completely ligated, and an improvement in LC function was seen. Our model of critical constriction differs from this model of coronary ligation; no significant improvement in LC function was seen with ischemia of the LAD segment. Only at the highest halothane concentration (stage IV) during phase 2 (critical constriction) was the depression of SS of the nonischemic segment (LC) substantially less than in phase 1 (control) (Fig. 2). This coincides with the appearance of dysfunction in the LAD region. With the addition of oxprenolol, the difference disappeared. The improvement in regional function of the normal segment when a compromised segment exhibits dysfunction may be due to intraventricular blood shunting resulting from increased compliance in the ischemic LAD region and subsequent afterload reduction of the nonischemic LC region, as has been postulated by Lew et al. (21). Oxprenolol abolishes this difference, possibly as a result of improved function, and thus there is a return toward a normal compliance in the LAD segment.

The application of critical constriction to a coronary artery of the dog heart is an approximation of the coronary stenosis seen in a human heart when angina pectoris is present. The fact that regional dysfunction occurs with anesthesia in the presence of critical constriction has been previously reported (4). We have shown that the addition of oxprenolol causes improvement in regional function such that the ischemic region can return to a level of function similar to a

nonischemic segment. This may be a specific property of oxprenolol, peculiar to β-blockers with ISA, or a general property of β-blockers. This study indicates a beneficial effect of β-blockade on the performance of compromised myocardium under halothane anesthesia, where regional dysfunction is minimized and systolic function improved. Delineation of the mechanism of protection of β-blockade and its relevance to clinical anesthesia in patients with coronary artery diseases awaits further studies.

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Postoperative Analgesia Induced by Subarachnoid Lidocaine plus Calcitonin

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A randomized double-blind study tested the analgesic effects of subarachnoid administration of salmon calcitonin (sCT) in acute postoperative pain. Sixty patients were grouped according to type of surgery (intraabdominal, extraabdominal, and lower extremities), subdivided into those given subarachnoid lidocaine 1 mg/kg plus sCT (100 IU) or lidocaine plus saline. Pain was evaluated by a descriptive scale 3, 6, 12, 24, 48, and 72 hr after surgery, as well as by the frequency of the patients' requests for postoperative analgesics. In all instances, the sCT-treated patients had significantly less postoperative pain. Similarly, the requests for analgesics was significantly lower or absent in the sCT-treated group. Minor side effects such as nausea and vomiting, abdominal pain, and "nervousness" were observed in a small number of sCT-treated patients. In our series of 30 patients, subarachnoid administration of sCT was an effective analgesic with minimal side effects. Its safety remains to be proved by further studies.

Key Words: PAIN—postoperative. PHARMACOLOGY—calcitonin.

Recent advances in the understanding of the pathways for pain transmission and perception have allowed the introduction of new methods for the treatment of acute and chronic pain (1). Although the endogenous opioid system is the main modulator of pain perception, other endogenous neurochemical systems may also play important physiological roles in analgesia. The finding of opioid receptors in the dorsal horn of the spinal cord was the basis for the subarachnoid and epidural administration of opiates in the treatment of pain. Such a route of administration can, however, be associated with severe side effects, including respiratory depression (2). Thus alternative methods that produce adequate analgesia and a low incidence of unwanted complications are worth investigating.

Among the possible nonopioid endogenous analgesic systems, calcitonin (CT) is a candidate with enough potential for clinical usefulness to warrant its study. A polypeptide hormone (3) found in mammalian brain (4), cerebrospinal fluid (5), and pituitary (6), CT is involved in calcium and phosphate metabolism (7). Its presence in nervous tissue suggests that CT may have a range of action that exceeds its role in calcium and phosphorus metabolism, a role that perhaps may be related to neurotransmission. Prolonged analgesia in animals (8) and humans (9) has, for example, been observed after the intrathecal administration of CT. Since the CT-induced analgesia is not modified by opioid antagonists, a nonopiate analgesic pathway could be involved (10). Human studies have used salmon CT (sCT) in the management of chronic pain associated with bone disease (11) or bone cancer (12) by various routes of administration (13) and by subcutaneous administration in acute postoperative pain not related to bone disease (14). The aim of the present study was to establish, in a double-blind trial, the analgesic effect of sCT after subarachnoid administration in acute postoperative pain.

Methods

Sixty male and female ASA I–II patients undergoing lower extremity ($n = 17$), extraabdominal (TURP, hemorrhoidectomy, etc., $n = 35$) or intraabdominal (appendectomy, oophorectomy, etc., $n = 10$) surgery were entered in the study. Informed consent was obtained from all patients during the preoperatory clin-

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Table 1. Demographic Data

Group	Sex (M/F)	Age (yr) ± SEM	Weight (kg) ± SEM	Type of surgery (n) Extremities	Extraabdominal	Intraabdominal
Control	16/14	73.1 ± 1.2	66.2 ± 1.4	8	18	4
S-calcitonin	15/15	72.3 ± 1.3	65.4 ± 1.8	9	15	6

ical evaluation and approval obtained from the Institutional Committee for Human Studies. Patients had spinal anesthesia with a 22- or 25-gauge needle at the L2–L3 interspace in the sitting position using a midline approach. All patients received lidocaine 1 mg/kg from a packaged preparation containing lidocaine 5%, dextrose 7.5%, and distilled water (Roger Bellon SA, France) plus 0.1 mg of epinephrine, and the volume was adjusted to 2 ml with dextrose 7.5%.

Patients were randomly assigned to a control group given lidocaine with epinephrine in dextrose 7.5% plus 1 ml of normal saline or an sCT group given the same dose of lidocaine with epinephrine in dextrose 7.5% plus 100 IU of sCT (salmon calcitonin, Sandoz) in 1 ml of normal saline. Both groups received a final volume of 3 ml.

Patients did not receive additional analgesics or sedatives during surgery. Age, weight, sex distribution, and duration of surgery were not different in the two groups. Pain was evaluated 3, 6, 12, 24, 48, and 72 hr after surgery. An observer who was not aware of the group to which a patient was assigned (control or sCT) questioned the patients regarding the intensity of pain and graded the pain as follows: 0 = no pain, 1 = slight, 2 = moderate, 3 = severe, and 4 = intolerable. Three different blinded observers evaluated our patients. Patients were also blinded as to which medication they had received. Side effects such as allergic reactions, nausea and vomiting, headache, or pruritus were also recorded. All patients were free to request analgesics (1 g dipyrone intramuscularly) as necessary, and the number of requests during the first 72 hr after surgery was recorded. Results were analyzed by two-way analysis of variance (15).

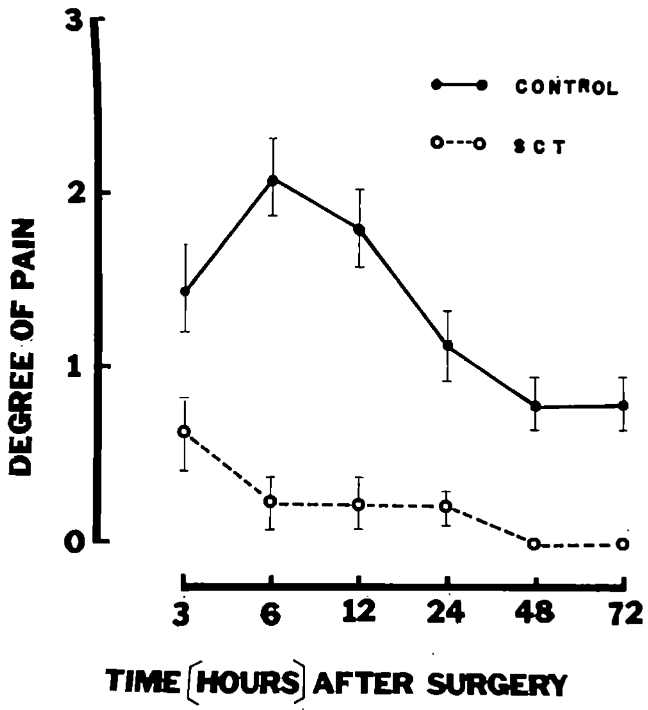

Figure 1. Degree of pain during the first 72 postoperative hours with and without intrathecal sCT based on a pain scale graded 0, no pain; 1, light; 2, moderate; 3, severe; and 4, intolerable pain. All points represent mean values (n = 30) and vertical bars indicate SEM. At all times, the observed degree of pain was significantly less in patients given sCT ($P < 0.02$ or less).

Results

Table 1 shows the distribution of patients in each group according to type of surgery. There were no differences in age, sex, or weight between groups. Spinal anesthesia was adequate in all instances, and both onset of anesthesia (3–5 min) and duration of surgery (68 ± 20 min) were similar in both groups.

Figure 1 shows that the degree of pain observed in both groups during the first 72 hr after surgery was significantly lower in the sCT-treated patients at all times. The greatest level of pain occurred 6 hr after surgery in the control group and persisted for 72 hr (Fig. 1). On the other hand, sCT-treated patients had significantly less pain at 6 hr and no pain after 48 hr. Similarly, requests for analgesics were significantly less frequent in the sCT-treated group during the first 72 hr after surgery: 1.8 ± 0.4 requests in control subjects (16 patients requested analgesics for a total of 54 times) and 0.2 ± 0.1 requests in patients given sCT (four patients for a total of six times) ($P < 0.001$). No significant differences in degree of pain and analgesia were observed between female and male patients in each group (data not shown).

When patients were compared according to type of surgery, the greatest pain was observed after intraabdominal surgery, followed by extraabdominal and surgery of the extremities in both groups. In patients

Table 2. Degree of Pain in Patients after Intraabdominal Surgery

Hours after operation	Degree of pain: Control	Degree of pain: S-calcitonin
3	2.0 ± 1.1	0.7 ± 0.7
6	3.2 ± 0.5	0.7 ± 0.7
12	3.5 ± 0.5	1.2 ± 0.5
24	3.0 ± 0.4	0.3 ± 0.3
48	1.8 ± 0.3	0
72	1.3 ± 0.6	0

Pain was evaluated by a single descriptive scale (see Methods). Number of patients in control group = four and in sCT = six. Values are given as the mean ± SEM. All SCT values are significantly different from control except at 3 hr postoperatively ($P < 0.05$).

Table 3. Requests for Analgesics during the Postoperative Period (72 hr) in Control and sCT-Treated Patients

Type of surgery	Control	S-calcitonin	P value
Extremities	1.25 ± 0.72	0	$P < 0.05$
Extraabdominal	1.22 ± 0.33	0.23 ± 0.12	$P < 0.001$
Intraabdominal	5.50 ± 1.19	0.50 ± 0.50	$P < 0.001$

Expressed as mean ± SEM.

having extraabdominal or extremity surgery, sCT analgesia was complete at 6 hr, without further pain thereafter (data not shown). Table 2 shows the degree of pain in the control and sCT-treated groups in patients undergoing intraabdominal surgery. At all time points scored, except at 3 hr after surgery, the degree of pain was significantly lower in sCT-treated patients ($P < 0.05$).

Table 3 shows the number of requests for analgesia by the patients in both groups, subdivided by type of surgery. As was the case with the degree of pain, the requests for analgesics were more frequent in the control intraabdominal group than in the sCT group. Patients treated with sCT in all three categories of operations had significantly fewer requests for analgesics (Table 3). Urinary output was 1.4 ± 0.12 L/24 hr in the control group and 2.6 ± 0.11 L/24 hr in the sCT-treated group ($P < 0.001$), with no differences between sex or type of surgery.

The observed side effects of sCT administration included mild abdominal pain that resolved after dipyrone administration (one patient, 3.3% of total), nausea and vomiting controlled by 10 mg of metoclopramide intravenously (two patients, 6.6%), and nine patients (29.7%) complaining of "nervousness" that resolved spontaneously at 6–12 hr and did not require treatment. No nausea and vomiting or "nervousness" was observed in the control group; those patients complained of pain related to the type and site of surgery, which was treated according to our protocol (see above). Neurological examinations performed in sCT-treated patients 1 week and 6 months after surgery were normal in all cases.

Discussion

The present study shows good analgesia and minimal side effects produced by the subarachnoid administration of sCT for relief of acute postoperative pain. This was also evidenced by a significant decrease in analgesic requirements during the first 72 hr after surgery in the patients receiving sCT. Our results have some limitations since pain evaluation was based on the opinions of an observer who questioned the patients regarding the intensity of pain. However, since both patients and observers were blinded and the differences in pain intensity and analgesic requirements highly significative among groups, we conclude that sCT is an effective analgesic in acute postoperative pain.

The mechanisms of sCT-mediated analgesia are undefined. Specific binding sites for CT have been demonstrated in mammals both in the spinal cord and in supraspinal central nervous system (CNS) centers related with pain transmission (16–19). The correlation between the analgesic activity and the localization of CT-binding sites in the appropriate CNS areas related to sensory transmission suggest a role of CT as an additional possible endogenous modulator of pain, and perhaps other sensory pathways. Since CT analgesia is not reversed by naloxone (20) or levalorphan (21) in experimental animals, an opioidlike mechanism of action can be excluded. Moreover, no changes in immunoreactive beta-endorphin levels in plasma have been detected in humans after CT administration (22). However, CT may still be activating other endogenous opioid mediators less susceptible to naloxone antagonism, such as the effects mediated by delta or kappa opioid receptors. On the other hand, there is good evidence that the CNS serotoninergic system may be involved in CT-induced analgesia, since intracerebroventricular administration of CT in rats produces increased 5-HT levels in the CNS and the administration of 5-HT antagonists interferes with CT-induced analgesia (23).

In summary, although the exact mechanism of its action has not been defined at present, it is clear from our study that intrathecal CT is an effective analgesic for the relief of postoperative pain. Determination of its safety requires the study of a larger number of patients.

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Effect of Dopamine on Hypoxic-Hypercapnic Interaction in Humans

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SABOL SJ, WARD DS. Effect of dopamine on hypoxic-hypercapnic interaction in humans. Anesth Analg 1987;66: 619–24.

To investigate the effect of intravenous dopamine on the chemical regulation of ventilation, we studied the ventilatory responses to hypercapnic hypoxia during dopamine infusion. Intravenous dopamine (3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was administered to six healthy human subjects. Two hypoxic challenges ($PET_{O_2} = 52.5 \pm 2.5$ mm Hg, $SaO_2 = 88.8 \pm 2.2\%$; mean $\pm$ SD) were administered at three CO_2 levels ($PET_{CO_2} = 40.8 \pm 0.5, 45.6 \pm 0.2, 49.8 \pm 0.3$ mm Hg) to each subject. The ventilatory responses were quantified by calculation of slopes and intercepts of the relationship between minute exhaled ventilation ($\dot{V}E$) and arterial hemoglobin saturation (SaO_2), and by the relationship between this slope ($\Delta\dot{V}E/\Delta SaO_2$) and carbon dioxide tension. Dopamine caused a 77% reduction in $\Delta\dot{V}E/\Delta SaO_2$ (hypoxic sensitivity) during eucapnia, a 39.5% reduction in hypoxic sensitivity at $PET_{CO_2} = 46$ mm Hg, and 38% reduction at $PET_{CO_2} = 50$ mm Hg ($P < 0.05$). Dopamine also reduced normoxic ventilation at all carbon dioxide levels. There was a greater depression in $\dot{V}E$ during hypercapnia (25.7% reduction) than during eucapnia (12% reduction). This indicates that dopamine depresses the normoxic ventilatory response to carbon dioxide. Intravenous dopamine reduces the ventilatory response to both hypoxia and hypercapnia but preserves the augmentation of hypoxic ventilatory drive by hypercapnia.

Key Words: VENTILATION—dopamine. SYMPATHETIC NERVOUS SYSTEM—dopamine. HYPOXIA—dopamine and ventilation.

Many studies have established the effects on ventilation of drugs used in anesthesia (1–4); see also (5) for a recent review. Several anesthetics, which are known respiratory depressants (1,3), have also been observed to reduce the augmented ventilatory response to combined hypoxia and hypercapnia. Knill and Gelb (1) reported a halothane-induced decrease in the ventilatory response to hypoxia, and instead of augmentation with hypercapnia, found a decrease in ventilation. This effect was attributed to a direct depression of the peripheral chemoreceptor by halothane.

Dopamine is used frequently both during anesthesia and the immediate postoperative period to provide inotropic support to critically ill patients. Intravenous dopamine blunts the ventilatory response to hypoxia (6,7) by inhibiting, in animals, neural discharge from the carotid body (8). The evidence in humans is indirect but also suggests that dopamine inhibits arterial peripheral chemoreceptor activity (6,7).

There are two reasons for studying dopamine's effects on the ventilatory response to the combination of hypoxia and hypercapnia. The effect of intravenous dopamine on the interaction of hypoxic and hypercapnic stimuli to ventilation is clinically important. Depression of the chemoreceptor reflex may increase the risk for development of hypoxemia and carbon dioxide retention, both common complications of anesthesia. We postulated that the pattern of ventilatory depression caused by hypoxic hypercapnia during halothane inhalation may also occur during dopamine infusion if depression in both cases was due to an effect on the peripheral chemoreceptor.

In addition, endogenous dopamine is present in the carotid body of several mammalian species, including humans (9–11), where it is postulated to be a neurotransmitter (9). Studying the effects of the interaction between hypoxic and hypercapnic stimuli in the presence and absence of intravenous dopamine may yield information about the physiologic role of a substance that is naturally occurring in the organ known to be a major site of interaction between the stimuli (12).

Methods

Six healthy male adult volunteers were studied with a UCLA Human Subjects Protection Committee-approved experimental protocol. Each subject was

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brought in before the day of testing to familiarize him with the equipment and experimental procedure. Subjects were informed that they would experience increased breathing but they were ignorant of the specific purpose of the experiment or the expected effect of dopamine. All subjects were asked to refrain from stimulant and depressant substances (tea, coffee, cola, marijuana, and alcoholic beverages) for 12 hr prior to the experiment. During experiments, subjects were seated and heart rate was monitored by electrocardiogram. With a nose clip in place, subjects breathed from a mixing chamber through a mouthpiece and a digital volume transducer with a bidirectional impeller to measure inhaled and exhaled volumes (Alpha Technologies VMM 110 Series Ventilation Measurement Module). Oxygen and carbon dioxide concentrations in the mixing chamber were measured with an Applied Electrochemistry Fuel Cell Analyzer (S3A) and a Beckman LB-2 infrared analyzer, respectively. Inspired and end-tidal oxygen and carbon dioxide concentrations were analyzed by mass spectrometer (Perkin-Elmer model 1100 Medical Gas Analyzer). Inspired concentrations of oxygen and carbon dioxide were adjusted by computer (DEC PDP-8/e) through evaluation of end-tidal gas on a breath-by-breath basis. Achievement of desired end-tidal conditions was brought about through a combination of feedback and feedforward control according to a technique described by Swanson and Bellville (12).

Minute exhaled ventilation was calculated on a breath-by-breath basis. All gas volumes were corrected to body temperature, ambient pressure, saturated (BTPS) conditions. Arterial hemoglobin saturation was monitored by ear oximeter (Hewlett-Packard model 47201A). These data were monitored on a strip chart recorder and collected by computer (DEC LSI-11/23).

Saline was infused at 25–50 ml/hr through an 18-gauge catheter in a large vein throughout all experiments. Dopamine was mixed in saline at 400 mg/L dilution and added to the intravenous solution via a Harvard Pump Syringe at a rate of 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The arrangement of the infusion pump and breathing apparatus made it possible to turn dopamine on and off without a subject's awareness.

Six hypoxic tests were performed on each subject on a single day, both with and without a dopamine infusion. The subjects were gradually rendered hypoxic at each of three preexisting end-tidal carbon dioxide tensions: $P_{ET_{CO_2}}$ of 40, 45, and 50 mm Hg. Three minutes of ventilation at eucapnia (40 mm Hg) and 9 min of ventilation at the hypercapnic levels (45 and 50 mm Hg) were used to ensure stable carbon dioxide level before hypoxic ramps began. The sequence of experiments progressed from eucapnic to hypercapnic levels. This sequence was used to eliminate any disequilibrium of brain tissue carbon dioxide due to inadequate washout between experiments.

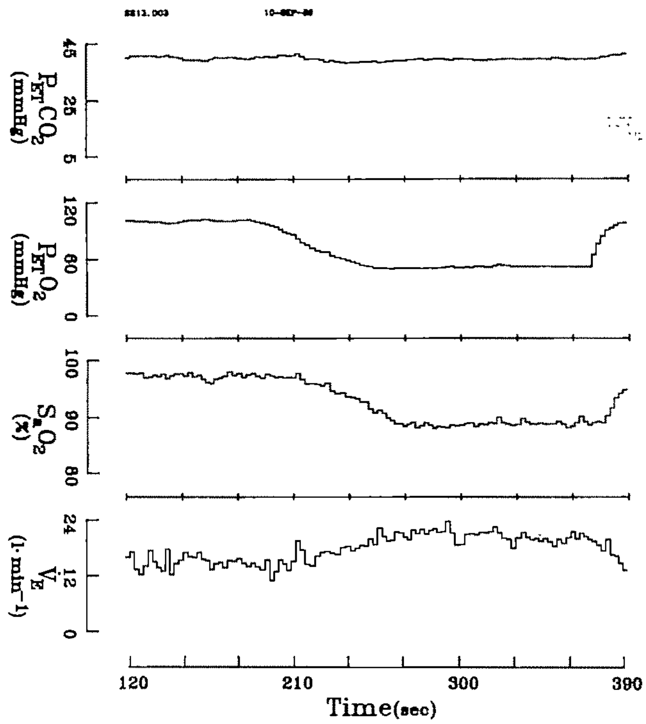

Figure 1. Record of breath-by-breath measurements for one hypoxic challenge is shown. From top to bottom the panels are: $P_{ET_{CO_2}}$, $P_{ET_{O_2}}$, Sa_{O_2} (ear oximeter), and $\dot{V}_E$.

At a constant $P_{ET_{CO_2}}$, end-tidal oxygen tension ($P_{ET_{O_2}}$) was lowered from approximately 100 to 50 mm Hg over 1 min and was followed by 2 min of constant hypoxia. After an abrupt return to normoxia and 3 min of normoxic breathing, the hypoxic ramp was repeated. Some 10–20 min were allowed between each test for subject comfort. Each subject performed one test with dopamine infusing (dopamine run) and one test without dopamine infusing (control run) at each $P_{ET_{CO_2}}$ level. The order of the two tests was random: half of the subjects performed dopamine runs first and half performed control runs first. The rapid onset and metabolism of intravenous dopamine made this arrangement possible. The time periods between tests were of sufficient length to ensure both that all infused dopamine had been metabolized prior to a control run and that a sufficient plasma level of dopamine had accumulated prior to a dopamine run (13).

The breath-by-breath data on each subject were averaged over 1-min intervals. The final 1 min before the beginning of the hypoxic ramp was compared for tidal volume (V_T), minute exhaled ventilation ($\dot{V}_E$),

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Table 1. Average Responses to Hypoxia[a]

	PET_{CO_2} (mm Hg)	PET_{O_2} (mm Hg)	SaO_2 (%)	VT (L)	$\dot{V}E$ (L/min[a])
Control period					
Saline	40.6 ± 1.0	96.6 ± 0.6	96.4 ± 1.4	0.73 ± 0.20	12.4 ± 3.4
Dopamine	42.0 ± 1.4[b]	97.1 ± 1.2	96.7 ± 0.5	0.62 ± 0.17[b]	10.3 ± 1.4[b]
Hypoxic period					
Saline	39.4 ± 0.6	56.3 ± 2.6	89.3 ± 1.3	0.91 ± 0.31	15.5 ± 3.2
Dopamine	41.0 ± 1.2[b]	55.0 ± 1.7	88.1 ± 0.6[b]	0.70 ± 0.22[b]	11.2 ± 1.5[b]
Control period					
Saline	45.6 ± 0.2	96.3 ± 0.3	97.5 ± 1.4	1.31 ± 0.37	26.1 ± 8.4
Dopamine	45.6 ± 0.2	96.6 ± 0.7	96.8 ± 1.7	1.01 ± 0.29[b]	19.1 ± 5.9[b]
Hypoxic period					
Saline	45.5 ± 0.5	56.9 ± 4.0	90.7 ± 1.6	1.75 ± 0.68	32.3 ± 10.0
Dopamine	45.6 ± 0.3	55.6 ± 1.1	89.2 ± 3.0	1.23 ± 0.33[b]	23.3 ± 7.1[b]
Control period					
Saline	49.2 ± 0.1	96.5 ± 0.4	97.1 ± 2.5	1.86 ± 0.46	40.5 ± 12.4
Dopamine	49.9 ± 0.2	96.3 ± 0.5	97.4 ± 1.6	1.57 ± 0.42[b]	30.8 ± 8.0[b]
Hypoxic period					
Saline	49.7 ± 0.5	56.6 ± 2.5	90.0 ± 2.9	2.31 ± 0.66	50.2 ± 14.4
Dopamine	49.7 ± 0.4	56.4 ± 2.3	90.0 ± 2.1	1.80 ± 0.37	36.5 ± 8.3[b]

[a]Average values during the 1-min interval before the hypoxic challenge (control period) and during the last 1-min interval of the hypoxic period at the three CO_2 levels for both control and dopamine infusion. Means ± SD of six subjects, two challenges each, are given (the intersubject standard deviation is used, ignoring the intrasubject breath-by-breath variability within the 1-min intervals).

[b]$P < 0.05$, dopamine infusion different from corresponding saline infusion period, paired *t*-test with Bonferroni correction for six comparisons.

and arterial hemoglobin saturation (SaO_2), with the final 1 min of constant hypoxia in each hypoxic response. As done by Rebuck and Campbell (14), we have assumed a linear relationship between minute ventilation and measured arterial hemoglobin saturation. The ventilatory responses to hypoxia were quantified by hypoxic sensitivity, the increase in ventilation for the decrease in saturation ($\Delta\dot{V}E/\Delta SaO_2$) at each level of PET_{CO_2}. Statistical comparisons were performed by paired *t*-test with significance at the 0.05 level, using the Bonferroni correction as appropriate.

Results

Figure 1 shows a computer-generated breath-by-breath plot of the first control hypoxic challenge in one subject. PET_{CO_2} is held constant while PET_{O_2} is lowered to approximately 52 mm Hg over 1 min. The arterial hemoglobin saturation mirrors this decline and an increase in $\dot{V}E$ is seen.

Table 1 summarizes the average responses for both control and dopamine runs at each carbon dioxide level. The end-tidal carbon dioxide levels achieved during dopamine and control runs were not significantly different except at the low carbon dioxide level. In those runs, PET_{CO_2} was about 1.5 mm Hg higher during dopamine runs than during control runs. During normoxia, decreased ventilation with dopamine led to an increase in PET_{CO_2} that could not be reduced since inspired carbon dioxide concentration was already zero. From Table 1 it can be seen that independent of carbon dioxide tensions, end-tidal oxygen tensions were comparable during control and dopamine runs, and vice versa. Increased ventilation during hypoxia was potentiated by hypercapnia both with and without dopamine infusion. Most of the ventilatory responses were due to changes in tidal volume rather than to changes in ventilatory frequency.

Figure 2 demonstrates the average response to hypoxia at each of the three carbon dioxide levels for the saline infusion (solid lines) and the reduction caused by dopamine (broken lines). Dopamine reduced nonhypoxic ventilation (right-hand data points), especially during hypercapnia.

Figure 3 shows, for each subject, the effect of dopamine on the ventilatory response to hypoxia as characterized by the slope of the line relating $\dot{V}E$ to SaO_2, $\Delta\dot{V}E/\Delta SaO_2$. The increase in ventilation as saturation decreased (hypoxic sensitivity) became less during dopamine infusion but no decrease in ventilation with hypoxia was seen. One subject (panel 3) had an increase in hypoxic sensitivity during dopamine infusion at PET_{CO_2} = 50 mm Hg. Dopamine reduced the increase in hypoxic sensitivity caused by carbon dioxide inhalation, but did not abolish it. Dopamine caused an average 77% decrease in hypoxic sensitivity during eucapnic ventilation, and an average 39.5% and 38% decrease at PET_{CO_2} 46 and 50 mm

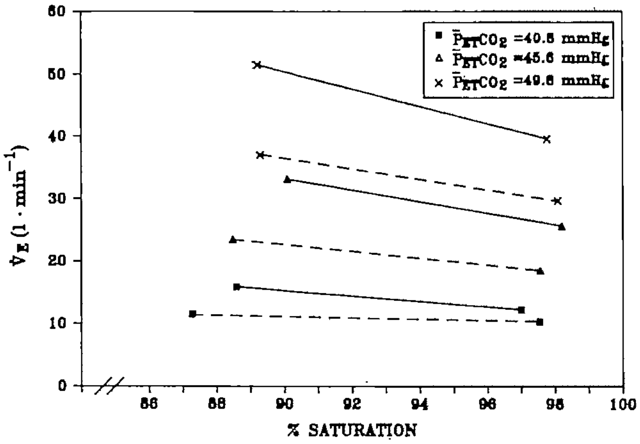

Figure 2. Average steady-state minute exhaled ventilation during normoxia and hypoxia, without (full lines) and with (broken lines) dopamine infusion. Each point is the average of six subjects, two hypoxic challenges each. Average $P_{ET_{CO_2}}$: 40.8, 45.6, and 49.8 mm Hg.

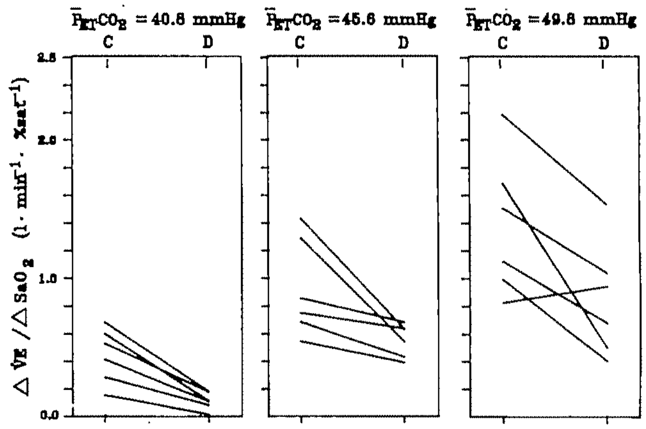

Figure 3. Hypoxic sensitivity ($\Delta\dot{V}_E/\Delta Sa_{O_2}$, L·min^{-1}·$Sa_{O_2}{}^{-1}$) for each subject at each $P_{ET_{CO_2}}$ level without (C) and with (D) a dopamine infusion. Average $P_{ET_{CO_2}}$ appears at the top of each panel. The average hypoxic sensitivities were (mean ± SD): at $P_{ET_{CO_2}}$ = 40.8 mm Hg: (C) 0.44 ± 0.22 and (D) 0.10 ± 0.10; at $P_{ET_{CO_2}}$ = 45.6 mm Hg: (C) 0.91 ± 0.35 and (D) 0.55 ± 0.19; at $P_{ET_{CO_2}}$ = 49.8 mm Hg: (C) 1.38 ± 0.57 and (D) 0.85 ± 0.47.

Hg, respectively. The decrease in hypoxic sensitivity was significant ($P < 0.05$) at all three CO_2 levels.

Discussion

Dopamine has previously been shown to blunt the ventilatory response to hypoxia during both eucapnia (7) and transient hypercapnia (15). It also blunts the portion of the carbon dioxide-induced ventilatory response attributable to peripheral chemoreceptors (16). That these studies reported different magnitudes of the effect of dopamine might be the result of methodological differences that make direct comparisons difficult. But the differences might also be due to the fact that these studies did not consider the possible effects of dopamine on the interaction between the two stimuli. The present study was undertaken to determine the effects of dopamine on this interaction.

Responses to intravenous dopamine must be interpreted with consideration of the dose of dopamine employed. The dose we chose (3 μg·kg^{-1}·min^{-1}) was based on past work using a similar dose (6,16) that did not cause any alteration in heart rate or arterial blood pressure, and that achieved the same ventilatory depression as other studies using a higher dose. Intravenous dopamine is known to cause circulatory changes at higher plasma concentrations, through stimulation of alpha and beta adrenergic receptors. Thus high dopamine doses (e.g., 10 μg·kg^{-1}·min^{-1}) may stimulate ventilation (7,17). We therefore used a dose thought to be high enough to stimulate dopaminergic receptors but low enough to minimize alpha- and beta-receptor stimulation. The absence of both changes in heart rate and of symptoms observed by Olson et al. (15), who used 5 μg·kg^{-1}·min^{-1}, indicate that this goal was achieved.

The results (Table 1) indicate that most of the ventilatory response to hypoxia resulted from an increase in tidal volume, which was attenuated by dopamine. There was also a smaller increase in respiratory frequency at high $P_{ET_{CO_2}}$. This agrees with our previous study (6) and the observation by Welsh et al. (7), but conflicts with results reported by Olson et al. (15), who found most of the dopamine effect to be due to changes in respiratory frequency. The speed of induction of hypoxia has been postulated by Olson et al. (15) to affect the ventilatory response, but we have observed a similar increase in tidal volume during both step (6) and ramp (this study) input profiles.

It is clear that the patterns of depression of the ventilatory response caused by dopamine infusion and halothane inhalation were not similar under the conditions studied. Whereas dopamine caused a blunting of the increase in hypoxic drive, the response to hypercapnic hypoxia was preserved. Halothane at 1.1 MAC abolished the reflex, ventilatory depression occurring as carbon dioxide tension increased (1). This suggests that the effects of halothane on the hypoxic ventilatory response are not due solely to action on the carotid body as suggested by Knill et al. (1), and that at least some of the effect of halothane on hypoxic-hypercapnic interaction also occurs outside the carotid body.

Dopamine also appeared in the present study to reduce normoxic hypercapnic ventilation, which agrees with our previous study (16). Welsh et al. (7), who

observed no effect of dopamine on hypercapnic ventilation, induced hypercapnia under hyperoxic conditions, which in itself suppresses the carotid chemoreceptors. We attempted to induce a hypercapnic stimulus that could be reproduced in control and dopamine runs. However, any effect of dopamine and/or hypoxia on central circulation might alter the time needed for equilibration between the central chemoreceptor environment and arterial blood. The PET_{CO_2} was similar in dopamine and control runs and all subjects reached a steady level of ventilation prior to hypoxic challenge (during hypercapnia, average $\dot{V}E$ 2 min before hypoxic challenge was not significantly different from 1 min before). The Bohr effect, which will result in a somewhat lower arterial hemoglobin saturation during hypercapnia, thus underestimating the ventilatory response, should be minimal under normoxic conditions with 97–100% saturation.

Endogenous dopamine occurs naturally in the carotid body (18,19), where it is postulated to be a neurotransmitter (9). Release of dopamine in the carotid body has been associated with reduced carotid sinus nerve activity (19). Intravenous dopamine leads to a similar reduction in neural output (20). It is tempting to speculate about the role of endogenous dopamine from experiments using intravenous dopamine. However, such speculation must be cautious. The functional role of endogenous dopamine in the carotid body is not well defined. Endogenous dopamine is a catecholamine, the effects of which are modulated by synthesis, reuptake, and catabolism at specific sites (19). In addition, evidence suggests the presence of two types of dopaminergic receptors in the cat carotid body, one inhibitory and the other excitatory (20). Intravenous dopamine in low concentrations inhibits carotid sinus nerve activity but in high concentrations stimulates activity. A given infusion rate of dopamine may thus have different effects depending upon the oxygen and carbon dioxide tensions, which could determine the amount of endogenous dopamine present. Species differences in content and activity of carotid body dopamine (21,22), and differences in neural output and ventilatory effect of intravenous dopamine (23) have limited the attempt to extrapolate to humans in whom evidence of dopamine activity and chemoreceptor activity remains indirect. And, finally, there are also other catecholamines active in the carotid body, including norepinephrine and possibly epinephrine (19), that could affect ventilation through a change in sympathetic nervous activity. With these limitations in mind, Lahiri et al. (24) made the interesting observation that dopamine blockade in cats increases the likelihood of respiratory oscillations, particularly during hypoxia. Modeling studies (25) predict that an increase in hypoxic sensitivity would cause instability in the respiratory control system. The role of dopamine could be to add stability to this system by modulating the ventilatory response to hypoxia.

The peripheral chemoreceptor functions as the sole mediator of hypoxic hyperventilation and is an important (26,27), if not the exclusive (12,28), mediator of the potentiating effect of hypercapnia on hypoxic ventilatory drive. However, steady-state ventilatory studies such as this one are not able to locate the site of interaction between intravenous dopamine and the hypoxic and hypercapnic stimuli to ventilation. There may be central nonadditive interactions between hypoxia and carbon dioxide, both stimulatory and depressive, although the data are conflicting (12,26,27). Therefore, the amount of total ventilation available for depression by dopamine is unknown. It is clear that critically ill patients can be adversely affected by dopamine administration (29) and should be watched for signs of respiratory failure, but it is also clear that dopamine does not cause the abolition of hypoxic drive during hypercapnia as was found with halothane and enflurane. The augmentation of hypoxic drive by hypercapnia exists during dopamine administration, even at high carbon dioxide levels.

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Midazolam as an Induction Agent in Children:
A Pharmacokinetic and Clinical Study

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SALONEN M, KANTO J, IISALO E, HIMBERG J-J. Midazolam as an induction agent in children: a pharmacokinetic and clinical study. Anesth Analg 1987;66: 625–8.

The pharmacokinetics of midazolam was studied in 21 children undergoing elective surgery at five different dose levels for induction of general anesthesia and were compared with a control group (n = 6) given thiopental, 5 mg/kg. The clearance of midazolam was found to be dose-related. The elimination half-life varied from 0.79 to 2.83 hr, which is shorter than in adult patients. Even a dose of 0.6 mg/kg midazolam was found to be unreliable as an agent for induction of anesthesia. Compared with thiopental 5 mg/kg, significantly longer times of onset to closing of the eyes (P < 0.01) and the disappearance of eyelid reflex (P < 0.01) were seen with midazolam.

Key Words: HYPNOTICS, BENZODIAZEPINES—midazolam. INDUCTION, ANESTHESIA—midazolam. ANESTHETICS, INTRAVENOUS—benzodiazepines. ANESTHESIA—pediatric.

The first water-soluble 1,4-benzodiazepine derivative, midazolam, has proved to be a satisfactory agent for induction of anesthesia in adults in a number of studies (1,2). However, neither its usefulness as an induction agent nor its pharmacokinetics have been thoroughly studied in children. In an earlier study performed in our hospital (3), flunitrazepam was found to be unsatisfactory for induction of anesthesia in children. Its main disadvantages were its slow and varying onset of action and postoperative sedation of long duration. However, midazolam may be more satisfactory in children because of its more rapid onset and shorter duration of action in comparison with other parenterally administered benzodiazepines (1,2). Therefore we have studied the use of midazolam for induction of anesthesia in children. We were also interested in the kinetics of midazolam, because in children the pharmacokinetics of flunitrazepam differed from those in adult patients (3).

Patients and Methods

After the approval of the local ethics committee, 27 children undergoing elective surgery were included in our study. Informed consent was obtained from the parents. Patient characteristics are given in Table 1. In group 1 the lowest dose of 0.075 mg/kg IV midazolam was used in connection with topical anesthesia to gain experience about onset and duration of action of this agent. Because the drug failed to induce loss of consciousness, the dose was later increased to 0.15 mg/kg, 0.30 mg/kg, and 0.45 mg/kg IV. In random order, a comparison was performed between thiopental 5 mg/kg, and midazolam 0.6 mg/kg IV. Intramuscular atropine 0.01 mg/kg, and meperidine 1 mg/kg were administered about 60 min before the beginning of anesthesia. If the fixed dose of midazolam failed to produce anesthesia in 3 min, thiopental (1–5 mg/kg) was administered to induce loss of consciousness. In addition to the induction agent, anesthesia included 70% nitrous oxide in oxygen, meperidine 1 mg/kg, suxamethonium 2 mg/kg, and pancuronium 0.1–0.3 mg/kg. Occasionally, halothane was also used. Atropine 0.02 mg/kg and neostigmine 0.04 mg/kg were used to reverse the neuromuscular block. The times to spontaneous closing of the eyes and disappearance of the eyelid reflex were recorded after the administration of midazolam or thiopental IV.

Venous blood samples were drawn from a contralateral antecubital vein before midazolam administration and subsequently 3, 5, 10, 15, 30, and 45 minutes, and 1, 2, 3, 4, and 6 hours after the drug injection. Serum concentrations of midazolam (Fig. 1) were determined with gas-liquid chromatography (4). This

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Table 1. The Mean and Standard Deviation of Age, Weight, and Height of the Patients as a Function of Midazolam Dose

	0.075 mg/kg (n = 3)	0.15 mg/kg (n = 6)	0.3 mg/kg (n = 6)	0.45 mg/kg (n = 6)	0.6 mg/kg (n = 6)	Control (Thiopental) (n = 6)
Age (mean)	7.33	6.72	6.07	6.11	3.82	3.99
(SD)	6.66	5.94	4.59	1.67	3.24	1.69
Weight (mean)	32.8	28.0	21.6	22.3	15.9	17.5
(SD)	26.3	22.7	13.7	3.19	8.76	4.36
Height (mean)	130.2	117.5	110.6	118.0	98.1	101.9
(SD)	47.9	42.4	28.6	9.22	28.9	12.5
ASA class I	3	5	6	5	5	6
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method separates midazolam from its main metabolite, 1-hydroxymethyl-midazolam, and the day to day and within day coefficient of variation ranges from 7 to 9%. The lower limit of sensitivity is 2–3 ng/ml serum or plasma. The pharmacokinetic parameters of unchanged midazolam were calculated as described in our earlier works (4–6): The area under the serum concentration curve (AUC) was calculated according to the trapezoidal method, with an extrapolation to infinity. AUC values were used to determine the apparent total distribution volume (VD = dose/β × AUC) and the total serum clearance (Cl = dose/AUC).

The statistical analysis of the data was carried out using one-way analysis of variance (ANOVA) and Kruskal-Wallis nonparametric ANOVA as well as Mann-Whitney U-tests. A multiple linear regression program was used to evaluate correlations. A value of $P < 0.05$ was considered as statistically significant.

Results

Our pharmacokinetic findings are summarized in Table 2. According to the one-way ANOVA, clearance is dose-dependent ($P < 0.01$). Because the variance of the lowest dose group differs significantly from that of the highest dose group (F-test), Kruskal-Wallis nonparametric ANOVA was employed as well. It gave a consistent probability value of 0.011. The other parameters were not affected by the dose. The mean serum concentration curves are presented in Figure 1. There was no correlation between age and V_β, t_β, or total serum clearance of midazolam. The correlation (r^2 = 0.42) between the dose and the clearance of midazolam is presented in Figure 2. To exclude the possible additional variables of age and weight as causes of the variation of midazolam kinetics, a multiple linear regression analysis was performed. This revealed a significant correlation between dose, age and weight, and drug clearance. The respective t values for the parameters are 3.46, 0.08, and 0.88, indicating that

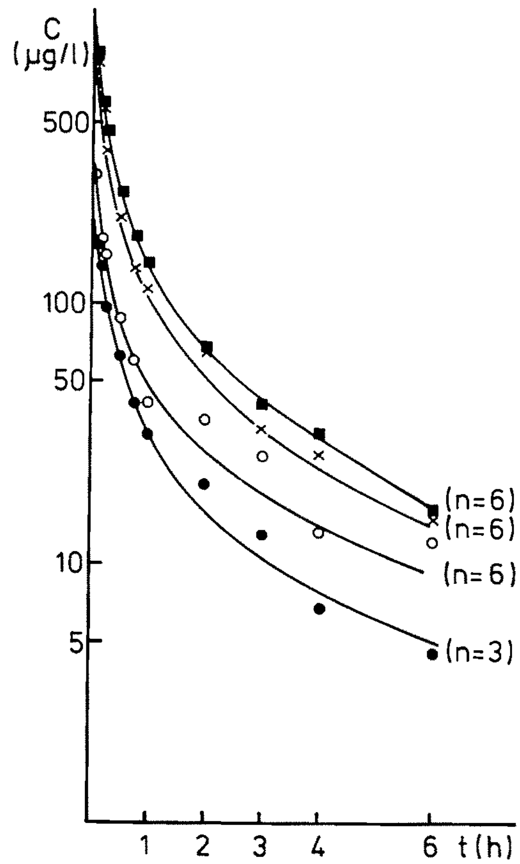

Figure 1. Midazolam serum time-concentration curves at four different dose levels (from 0.075 to 0.45 mg/kg). Presented are mean values. Three-minute time point is omitted for clarity. ● — ● = 0.075 mg/kg; ○ — ○ = 0.15 mg/kg; x—x = 0.3 mg/kg; ■ — ■ = 0.45 mg/kg IV.

age and weight are not important in explaining the correlation. A statistically significant difference was detected between midazolam 0.6 mg/kg and thiopental groups in the times to closing the eyes ($P < 0.003$, Mann-Whitney U-test) and disappearance of eyelid reflex ($P < 0.01$), Mann-Whitney U-test). There were no statistically significant changes in these times with

Table 2. The Pharmacokinetic Parameters of Midazolam in Children at Different Dose Levels

	0.075 mg/kg (n = 3)	0.15 mg/kg (n = 6)	0.3 mg/kg (n = 6)	0.45 mg/kg (n = 6)	F value
$T_{\frac{1}{2}\alpha}$ (min)	5.26 ± 4.92	2.18 ± 3.46	5.39 ± 3.16	4.89 ± 2.19	1.21
$V_{D\alpha}$ (L/kg)	0.31 ± 0.14	0.13 ± 0.31	0.20 ± 0.11	0.27 ± 0.10	0.85
$T_{\frac{1}{2}\beta}$ (hr)	1.41 ± 0.36	1.72 ± 0.62	1.42 ± 0.49	1.24 ± 0.29	1.03
$V_{D\beta}$ (L/kg)	1.38 ± 0.60	1.50 ± 0.46	1.46 ± 0.43	1.57 ± 0.47	0.13
Cl (ml·min^{-1}kg^{-1})	6.67 ± 5.50	4.83 ± 2.33	8.67 ± 2.50	11.2 ± 1.33	5.58^a
AUC (hr·μg·L^{-1})	138 ± 50.4	232 ± 40.0	486 ± 117.8	576 ± 89.2	27.9^b

One-way ANOVA F values and significance levels $^aP < 0.01$; $^bP < 0.001$.
Abbreviations: AUC, area under concentration curve; Cl, total midazolam clearance; $T_{\frac{1}{2}\alpha}$, distribution phase half-life of midazolam; $T_{\frac{1}{2}\beta}$, elimination phase half-life of midazolam; $V_{D\alpha}$, volume of distribution of α-phase; $V_{D\beta}$, volume of distribution of β-phase.

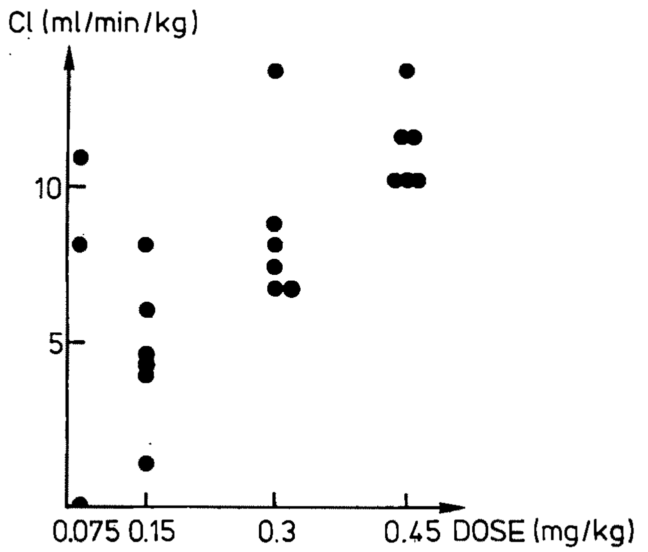

Figure 2. Individual clearances plotted against dose. Linear regression analysis yields the following equation: y = 0.22 + 0.98 * x. A significant correlation was detected, r^2 = 0.42; F value of regression = 14.0.

doses of midazolam between 0.15 and 0.45 mg/kg (Kruskall-Wallis test, Table 3).

Discussion

Earlier studies have shown an intersubject variation in the pharmacokinetics of midazolam with possible clinical consequences. Reduced elimination has been reported in elderly males (7), in obese subjects (7), in some healthy adults (8), and in patients undergoing cardiopulmonary bypass surgery (9), whereas increased elimination has been found in full term pregnant patients (6,10). Furthermore, the gastrointestinal absorption of this water-soluble benzodiazepine appears to be variable because of changes in gastrointestinal motility during pregnancy (6). The blood-flow dependent hepatic elimination of midazolam is even dependent on posture and circadian rhythm in hepatic enzyme activities (11). The reason for the variability in hepatic clearance may lie in pharmacogenetic variation, reduced liver blood flow, or in the effects of enzyme inhibitory or stimulatory agents (8,12). In patients with renal failure, the free fraction of midazolam in plasma was found to be increased, but after correcting individual kinetic values for the free fractions, the kinetics in the patients did not differ from the kinetics in healthy subjects (13). Recent reports (14) have shown that the pharmacokinetics of orally administered midazolam are probably dependent on the dose because of the saturation of the first-pass metabolism in the liver. In short, many factors affect the kinetics of midazolam.

Our results suggest that the kinetics of midazolam in children are dose-related. This has not been the case with other benzodiazepines studied so far (3). The dose dependency might be due to the changes in the free fraction of midazolam in plasma. If the proteins capable of binding midazolam became saturated, then the free fraction would increase, with a resulting increased rate of metabolism. On the other hand, our results might be affected by the anesthesia itself, so that after a smaller induction dose higher concentrations of other anesthetics for maintenance of anesthesia are needed, and these other anesthetic agents could affect the metabolism of midazolam in the liver. All in all, however, the elimination of this water-soluble benzodiazepine appears to occur faster in children than in adults (1,2,4,6). The fact that in our study a fraction of patients failed to fall asleep with midazolam alone is in disagreement with earlier studies (15,16). This may be due to our lighter routine premedication; nevertheless, benzodiazepines appear to have a slow and varying onset of action in children (3). Benzodiazepines appear to be more useful when used as an adjuvant to general or local anesthesia (1,2).

In conclusion, midazolam seems to be incapable of reliably inducing anesthesia in children premedicated with atropine plus meperidine. As a sole induction

Table 3. The Pharmacodynamic Results of Three Dose Levels of Midazolam and the Comparison between Different Doses of Midazolam and Thiopental

	Midazolam[a]			Midazolam[a]	Thiopental[a]
	0.15 ($n = 6$)	0.3 ($n = 6$)	0.45 ($n = 6$)	0.6 ($n = 6$)	5 ($n = 6$)
Time to closing of eyes (sec)	110 ± 17	77 ± 43	63 ± 34	108 ± 140	20 ± 3.2[b]
Disappearance of lid reflex (sec)	150 ± 43	153 ± 11	107 ± 80	122 ± 135	28.3 ± 6.5[b]
Fraction not sleeping with midazolam	5/6	4/6	2/6	2/6	—

[a]mg/kg.
[b] = $P < 0.01$, Student's t-test.

agent it is less reliable than thiopental. The kinetics of midazolam in children differ from that in adults and are possibly dose-dependent. The elimination half-life is shorter in children than in adults. This fact deserves consideration when prolonged residual effects are to be avoided. A possible dose-dependency of the kinetics of midazolam warrants further studies.

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Pain Threshold and Subjectively Perceived Epidural Sensory Blockade with 0.5% Bupivacaine

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PONHOLD H, WINKLER G, REHAK PH. Pain threshold and subjectively perceived epidural sensory blockade with 0.5% bupivacaine. Anesth Analg 1987;66:629–32.

We investigated the relationship between patients' pain thresholds and the quality of the subjectively perceived epidural sensory blockade (SPESB). The pain thresholds of 50 patients were evaluated with a modification of the submaximum effort tourniquet technique. There was a significant correlation between pain threshold and the number of subjectively perceived anesthetic and analgesic segments, the likelihood of developing an extensive SPESB being greater in patients with higher pain thresholds. Forty-one percent of patients with pain scores of less than 10 mm on the visual analogue scale, but no patient with a pain score of 20 mm or more, developed anesthesia in ten or more spinal segments.

Key Words: ANESTHETIC TECHNIQUES—epidural. PAIN—threshold.

Many factors governing the amount of local anesthetic needed for a particular level of epidural blockade have been described, including obesity, pregnancy, arteriosclerosis, height, and age of the patient (1). Although studies using standard techniques show significant differences between different groups, there are wide variations in anesthetic levels within each group of patients, e.g., age (2) and concentration (3). Hitherto unknown patient characteristics may be responsible for these variations. Thus, even in experienced hands, epidural blockade for a particular operation is not infrequently associated with an unintentionally low or high spread of subjectively perceived epidural sensory blockade (SPESB) (4).

In recent years many factors have been reported to modulate afferent impulses at virtually every synapse in the ascending pathway of the central nervous system (CNS). Modulating mechanisms, including antinociceptive neural pathways and chemical transmitters, have been proven to exist for the transmission of pain impulses (5). Recent investigations with somatosensory evoked potentials (6) and thermographic investigations (7) also indicate that during regional anesthesia nerve impulses from a peripheral region with effective subjectively perceived anesthesia may reach higher levels of the CNS. Antinociceptive mechanisms may play a role in suppressing nerve impulses that are not blocked by the local anesthetic. In the present study, we examined the relationship between patients' pain thresholds and the quality of SPESB.

Methods

Fifty patients who were scheduled for orthopedic surgery were studied. These patients were ASA classification 1–3, between 20 and 60 years of age, weighing 65–85 kg. All received 5–10 mg diazepam intramuscularly for premedication. Patients more than 10% above ideal weight (ideal weight in kilograms being height in centimeters minus 100), pregnant patients, and those with arteriocleroris or extremes of height (<165 cm, >180 cm) were excluded. Informed consent was obtained and the study fulfilled the guidelines of the Human Ethics Committee of the hospital.

The pain threshold was evaluated using a modification of the submaximum effort tourniquet technique (8). Because there are differences in the pain threshold between the dominant and nondominant arm (9), the nondominant arm was used throughout. A blood pressure cuff was wrapped around the upper arm. The arm was elevated for 1 min. The blood pressure cuff was then inflated to 250 mm Hg for 1 min. After deflation of the cuff, the patient was asked to rate his pain on a visual analogue scale (10) with a length of 100 mm. The distance of the patient's mark on the analogue scale from the "no-pain" end of the scale was measured in millimeters. The patient was then given an additional 5–10 mg diazepam IV. The

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dosage was indirectly proportional to the age of the patient. It was the aim of both doses of diazepam to have the patient awake with minimal anxiety when the quality of the blockade was tested.

An epidural catheter was placed at the L2-3 or L3-4 interspace and 0.5% bupivacaine was injected while the patient was in a supine horizontal position. The volume depended on the age of the patient (11). Patients between 20 and 30 yr received 20 ml, those between 30 and 40 yr received 18 ml, those between 40 and 50 years received 15 ml, and those between 50 and 60 yr received 13 ml. Three milliliters of each of these volumes were injected as a test dose. Two minutes later the remaining volume was slowly injected. Thirty minutes after the injection of the local anesthetic, each spinal segment upwards from the fifth sacral segment was tested with a sterile safety pin (12). The sharp and dull ends of the pin were used at random. Whenever the patient felt the pin, he was asked to describe what he felt and where he felt it. Care was taken that the safety pin was always used with the same pressure. A spinal segment was considered anesthetic when the patient did not feel the sharp end of the safety pin. It was considered analgesic when the patient described the sharp end of the pin as dull. The intensity of motor blockade was tested using the Bromage scale: 0, patient could raise his straight leg; 1, patient could elevate his knee; 2, patient could move only his foot; 3, no movement of the leg was possible (1). Only one author (H.P.) examined the extent of the SPESB and the intensity of motor blockade. He did not know the pain threshold of the patient. The patient did not know the purpose of the study.

Patients who did not develop an epidural blockade sufficient for surgery were given an epidural injection of 0.5% bupivacaine through the same epidural catheter 35 min after the first injection. The volume of the second injection was inversely related to the number of subjectively perceived anesthetic segments after the first injection. The aim was to reach a satisfactory blockade for the particular operation. Three patients had a third injection. Patients in whom the reinjection(s) did not lead to a sensory blockade were excluded from the study. In these patients it was assumed that the epidural catheter was not in the correct position. The results of the first injection were used for statistical analysis.

Spearman's rank correlation coefficient (corrected for ties) (13) was used to test for statistical significance of the relationship between pain scores and SPESB, extent of motor blockade and age. χ^2-tests were used to determine the relation between age-related dosage (1) and extent of the SPESB. $P < 0.05$ was considered statistically significant.

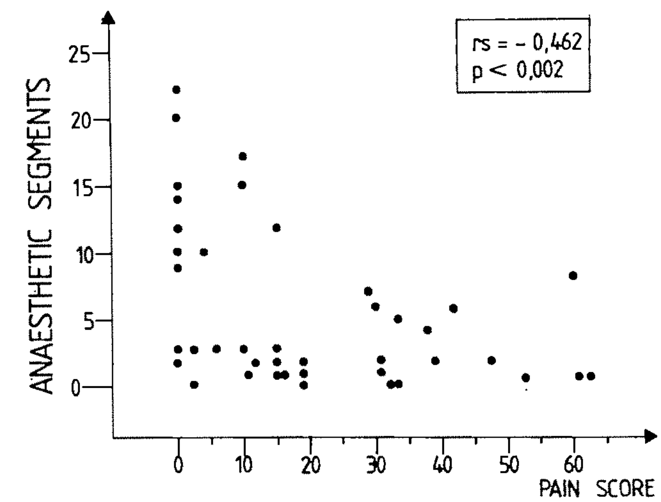

Figure 1. Correlation between pain score (millimeters on the visual analogue scale) and number of subjectively perceived anaesthetic segments during an epidural blockade with 0.5% bupivacaine. The likelihood of developing a large number of subjectively perceived anaesthetic segments was greater in patients with a low pain score. Some dots represent more than one patient (rs = Spearman's correlation coefficient, the proof and measurement of the correlation between two things).

Results

Subjectively perceived epidural sensory blockade: There was a significant correlation between the pain score and the number of anesthetic segments (Fig. 1). Forty-one percent of the patients with a pain score of less than 10 mm and 29% of the patients with a pain score of less than 20 mm developed ten or more anesthetic segments. No patient with a pain score of 20 mm or more developed ten or more anesthetic segments.

There was a significant correlation between the pain score and the number of analgesic segments (Fig. 2). Forty-one percent of the patients with a pain score of less than 10 mm and 30% of the patients with a pain score of less than 35 mm developed 14 or more analgesic segments. No patient with a pain score of 35 mm or more developed 14 or more analgesic segments. There was no significant correlation between the pain score and the intensity of motor blockade (Spearman's correlation coefficient = −0.223), and there was no significant correlation between the pain score and the age of the patient (Spearman's correlation coefficient = −0.060).

There was also no significant relationship between age and the distribution of patients into different classes according to whether the patients developed ten or

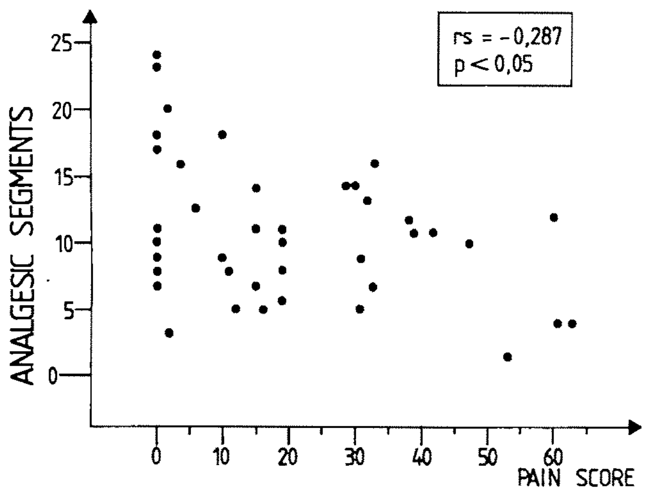

Figure 2. Correlation between pain score (millimeters on the visual analogue scale) and number of subjectively perceived analgesic segments during an epidural blockade with 0.5% bupivacaine. The likelihood of developing a large number of subjectively perceived analgesic segments was greater in patients with a low pain score. Some dots represent more than one patient (rs = Spearman's correlation coefficient, the proof and measurement of the correlation between two things).

more subjectively perceived analgesic or anesthetic segments, or whether they developed less than ten subjectively perceived analgesic or anesthetic segments (Tables 1 and 2).

Four patients failed to develop anesthesia in even one segment after the first epidural injection, although every patient developed analgesic segments. Second or third epidural injections in patients who developed an unsatisfactory blockade with the first injection resulted in an adequate SPESB for the scheduled operation except for one patient in whom a reinjection did not lead to a blockade and who was excluded from the study. It was assumed that the epidural catheter was not in the correct position in this patient.

Discussion

The absence of a significant correlation between pain score and motor blockade indicates that blockade of motor impulses by the local anesthetic does not differ significantly between patients with different pain scores. This finding suggests that blockade of sensory impulses by the local anesthetic does not differ significantly between patients with different pain scores either. There is also no reason to believe that the spread of a given volume of local anesthetic in the epidural space differs according to the pain score of the patient. For this reason, we assume that there is

Table 1. Distribution of Patients by Age and Number of Anesthetic Segments

	Number of anesthetic segments	
Age (yr)	0–9	≥10
20–40	27 pt	6 pt
41–60	13 pt	4 pt

χ^2 = 0.0056 (not significant).

Table 2. Distribution of Patients by Age and Number of Analgesic Segments

	Number of analgesic segments	
Age (yr)	0–9	≥10
20–40	14	19
41–60	7	10

χ^2 = 0.0474 (not significant).

no significant difference in the intensity of blockade of sensory impulses produced by the local anesthetic in patients with different pain scores. Recent investigations using somatosensory evoked potentials indicate that during an epidural anesthesia some impulses arising in the area of anesthesia do reach the cortex even in the presence of effective pinprick anesthesia (6). Thus even in the presence of good SPESB, not all sensory impulses may be prevented from reaching higher CNS levels. Those impulses that are not blocked by the local anesthetic are subject to modulating mechanisms. Modulation of afferent impulses by CNS inhibitory mechanisms occurs at virtually every synapse in the ascending pathway of the CNS (5). Those impulses that do reach higher synapses in the CNS can then be further modulated to different extents in different patients. It is possible that in some patients these impulses will be prevented from reaching high CNS levels and that in other patients, the same intensity of residual impulses may result in perceived touch or pain.

This investigation shows a significant correlation between the pain threshold and SPESB. Because the pain threshold very likely is an indicator of the quality of the patient's antinociceptive mechanisms (5), we can assume that there is a correlation between the quality of a patient's antinociceptive mechanisms and the extent of the SPESB. However, this investigation also shows wide variations in the spread of SPESB at each level of pain score, reflecting the fact that additional modulating mechanisms not tested in this investigation may also affect the quality of SPESB. Such wide variations of anesthetic levels have also

been reported by other investigators in spite of the use of standard techniques (2,3,14).

Considering the wide variations in SPESB, a single-injection epidural anesthesia seems inappropriate. A continuous technique permits a second injection without a second puncture in patients who fail to develop a sufficient SPESB after the first injection. Because patients with low pain scores have a good chance of developing an extensive SPESB, the dosage of the first epidural injection should be conservative in these patients. Because a higher concentration of a local anesthetic results in a more profound blockade of sensory impulses, more highly concentrated solutions might be indicated for the first epidural injection in patients with a high pain score. As reported before (3), our data also show that the epidural injection of 0.5% bupivacaine can result in the development of a blockade with analgesia but without anesthesia.

There was no significant age-related difference in the spread of the SPESB. Because there also was no significant correlation between pain score and age, the age-related dosage suggested by Bromage (11) and used in this study is confirmed.

The influence of additional modulating mechanisms on the quality of the SPESB also explains why although there is a correlation between the spread of a solution in the epidural space and the spread of the SPESB in some patients there are marked differences in others (15).

The present study further indicates that the blockade of sensory impulses by the local anesthetic during an epidural anesthesia does not necessarily have to be complete. It must be adequate for the particular patient. The impulses not blocked by the local anesthetic must not be stronger than the ability of the patient's modulating system to prevent the experience of touch or pain. Because the pain threshold is an indicator for part of the modulating system (5), it has an effect on the quality of the SPESB and can be used to identify patients with a likelihood of developing a large number of subjectively perceived anesthetic and analgesic segments during an epidural blockade with 0.5% bupivacaine.

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Relationship between Single Twitch Depression and Train-of-Four Fade:

Influence of Relaxant Dose during Onset and Spontaneous Offset of Neuromuscular Blockade

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POWER SJ, JONES RM. Relationship between single twitch depression and train-of-four fade: influence of relaxant dose during onset and spontaneous offset of neuromuscular blockade. Anesth Analg 1987;66:633–6.

The characteristics of the train-of-four (TOF) response were studied electromyographically during onset and spontaneous offset of neuromuscular blockade with bolus doses of vecuronium (ED_{95}, and $ED_{95} \times 2$). During onset of blockade there was less fade with the larger than the smaller dose of vecuronium, demonstrating a variable and dose-related relationship between the ratio of height of the initial twitch, T1, and fourth twitch, T4. With both doses TOF fade was more pronounced during recovery than during onset of block, but at the same T1 values during offset, both doses were associated with similar degrees of fade during recovery. Thus with bolus doses of vecuronium the T4 ratio during recovery bears a fixed relationship to initial T1 depression that is independent of dose.

Key Words: NEUROMUSCULAR RELAXANTS—vecuronium. MONITORING—electromyography, train-of-four.

The train-of-four (TOF) pattern of stimulation of peripheral nerves is often used to monitor the degree of neuromuscular blockade when anesthetic techniques include use of muscle relaxants. The ratio of the fourth to the first twitch in the train–the train-of-four (or T4) ratio–is one measure of the degree of paralysis. During spontaneous or pharmacologically induced offset of neuromuscular blockade a T4 ratio of 0.5–0.7 has been reported to be compatible with clinically safe degrees of return of neuromuscular transmission (1,2). However, a number of factors influence the degree of fade present at any one time, and during onset of block the degree of fade is markedly influenced by the dose of relaxant (3). If the degree of fade present during offset of block is similarly dose-related, and if a particular T4 ratio is used to indicate the need, or otherwise, for anticholinesterase administration, misleading and potentially dangerous conclusions may be drawn. We have thus studied the degree of fade present during spontaneous offset of neuromuscular block after initially administering two different doses of the muscle relaxant vecuronium.

Methods

After local ethical committee approval and with informed consent, 33 ASA class 1 and 2 adult patients scheduled for elective surgery requiring the use of neuromuscular blocking drugs were studied. None had neuromuscular or hepatorenal disease or were taking any medication known to influence neuromuscular transmission. All patients were within 20% of ideal weight. The nondominant arm was immobilized in a splint and used for hypothenar electromyographic monitoring. Train-of-four ulnar nerve stimulation was with supramaximal 0.1 msec square-wave impulses, repeated every 20 sec.

A standardized anesthetic technique was used. Patients were either unpremedicated or they received diazepam, 10 mg orally, approximately 1 hr before the operation. Anesthesia was induced with 4–6 mg/kg thiopental after 1 μg/kg fentanyl had been injected through an indwelling needle on the dorsum of the dominant hand. The patient then spontaneously breathed 66% nitrous oxide in oxygen with 1% inspired halothane delivered via a Bain-type coaxial breathing system and facemask. Baseline neuromus-

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Table 1. Demographic Data of the Patients

	Vecuronium	
	ED_{95}	$ED_{95} \times 2$
Number	11	11
Sex ratio (M/F)	5/6	4/7
Age (yr)*	30 ± 14	34 ± 13
Weight (kg)*	64 ± 9	61 ± 8

*Values are mean ± SD.

Table 2. Recovery Time to T1: Control 25, 50, and 75%

	Vecuronium	
Offset times (min)	ED_{95}	$ED_{95} \times 2$
T1: control 25%	15 ± 3	36 ± 7
T1: control 50%	19 ± 3	41 ± 8
T1: control 75%	22 ± 4	48 ± 9

Values are mean ± SD.

cular recordings were obtained and when they were stable, 0.05 mg/kg or 1.0 mg/kg vecuronium (approximately ED_{95} or $ED_{95} \times 2$) was injected, preceded and followed by 1 ml of normal saline. The relaxants were injected at the same rate, as a rapid bolus. Tracheal intubation was performed when the first twitch of the train (T1) was 5% of control or after 4 min, whichever was sooner. Anesthesia was maintained with 66% nitrous oxide in oxygen with 0.5% inspired halothane and incremental fentanyl as indicated. Intermittent positive pressure ventilation was maintained with a Nuffield 200 series anesthesia ventilator and a Bain-type circuit with fresh gas flow of 70 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$.

Twitch height was recorded during onset, spontaneous offset, and after anticholinesterase administration. Two indices of neuromuscular blockade were recorded: the ratio between the height of the first twitch (T1) before and after vecuronium (T1:control percent), and the ratio between the height of the fourth and the height of the first twitch response in the same train (T4 ratio). The records were judged to be suitable for analysis if T1 after evoked reversal was 90–110% of control T1. Comparisons of fade between relaxants were made at the T1 value nearest to 25% of control (T1:control 25%) during onset and at 25, 50, and 75% of control (T1:control 25, 50, and 75%) during spontaneous offset.

The results are expressed as means ± SD. Statistical analysis was done by nonparametric methods (Wilcoxon's rank sum test).

Results

Although 33 patients were studied, the records for only 22 patients were suitable for analysis based on the described criteria. Patients' age, weight, and sex are recorded in Table 1.

During onset of neuromuscular blockade at T1:control 25% the T4 ratio was 0.47 (0.09) for the ED_{95} group compared with 0.69 (0.1) for the $ED_{95} \times 2$ group. There was significantly less fade ($P < 0.01$) associated with the larger dose of vecuronium.

The times to return to all chosen offset T1:control values were longer in the group given the larger dose of vecuronium (Table 2).

When the degree of fade was compared at T1:control 25% during onset and spontaneous offset of neuromuscular blockade there was significantly more fade ($P < 0.01$) during offset than during onset for both doses of relaxant. At T1:control 25% the T4 ratio for vecuronium ED_{95} was 0.47 (0.09) during onset and 0.06 (0.09) during offset. The results for the larger dose demonstrated a similar pattern, with a T4 ratio of 0.69 (0.1) during onset compared with 0.02 (0.04) during offset.

However, when the T4 ratios were compared during spontaneous offset of neuromuscular blockade (Table 3) there were no significant differences in the degree of fade at the specified T1:control values between the two doses of vecuronium.

Discussion

Use of train-of-four pattern to monitor the degree of paralysis caused by muscle relaxant drugs during anesthesia was introduced by Ali et al. in 1970 (4) although it was first described by Roberts and Wilson for the assessment of myasthenic patients in 1969 (5,6). With this pattern of stimulation, the nerve (usually the ulnar nerve) is stimulated at half-second intervals for 2 sec and thus four pulses are delivered. This may be repeated every 10 or 20 sec or at longer intervals. Supramaximal stimuli are needed to ensure that the propagated nerve action potentials release sufficient quanta of acetylcholine to contract all the fibres in the stimulated muscle. In addition to its magnitude, the stimulus must have an appropriate duration to ensure that repetitive firing does not occur. It has also been found that supramaximal square wave stimuli of 0.1–0.2 milliseconds are usually best.

Using appropriate recording equipment (mechanomyography or electromyography) to determine the train-of-four ratio it has been reported that a value of between 0.5 and 0.7 indicates the safe return of muscle power after spontaneous or pharmacologically induced offset of neuromuscular blockade. At the pres-

Table 3. T4 Ratios at T1: Control 25, 50 and 75% during Recovery

Offset T4 ratio	Vecuronium ED_{95}	Vecuronium $ED_{95} \times 2$
T1: control 25%	0.06 ± 0.09	0.02 ± 0.04
T1: control 50%	0.12 ± 0.07	0.1 ± 0.04
T1: control 75%	0.21 ± 0.08	0.22 ± 0.07

Values are mean ± SD.

ent time this pattern of stimulation is regarded by some as being the most sensitive and practical method of determining the extent of drug-induced inhibition of normal neuromuscular transmission. The TOF pattern is more sensitive than single twitch monitoring, marked fade often being present (indicating residual receptor occupancy) when a single twitch has returned to control values. Also, the TOF does not require recording twitch response before relaxant administration. The TOF is additionally less painful than tetanic stimulation and, unlike some frequencies of tetanus, does not artificially shift responses towards normality (posttetanic facilitation).

Fade during high frequency stimulation, whether tetanic or train-of-four, may represent the action of muscle relaxants at sites other than the postsynaptic nicotinic receptor (7–11). One suggestion is that single-twitch depression is due to the action of the relaxant at the classical postjunctional receptor, but that fade represents drug action elsewhere, perhaps at prejunctional receptors (12) or ion channels (13), or even at another postjunctional site (14–15).

Whatever the mechanism underlying the presence of fade, its quantification is now widely used as a method of monitoring the effects of relaxant drugs and their antagonists both in research and (increasingly) in routine clinical monitoring. However, as we and other groups have reported, a number of factors influence the degree of fade present at any given time. Thus, fade is more pronounced during the offset of neuromuscular blockade than it is during onset (3,16–18). During spontaneous offset different relaxants are also associated with different degrees of fade, and this profile may not be similar to the fade profile obtained during onset of blockade (3).

Fade during onset of blockade is also known to be dose-related. We have previously reported that increasing the dose of atracurium reduces the amount of fade present during the onset of muscle paralysis and we have discussed the possible reasons for this (3). If a similar phenomenon occurs during spontaneous offset of neuromuscular blockade the use of a specific degree of fade to indicate adequate return of muscle power—for instance a T4 ratio of 0.5–0.7—might result in misleading conclusions being drawn concerning the adequacy or otherwise of neuromuscular transmission.

We have demonstrated again that fade is more apparent during offset than during onset, whatever the initial dose of relaxant administered. We have also confirmed our previous observation with atracurium-induced paralysis (3) that larger doses of relaxant—in this instance vecuronium—are associated with lesser degrees of fade during onset. During onset of block, therefore, the T4 ratio bears no fixed relationship to the height of T1. It is likely that both these observations are applicable to all competitive neuromuscular blockers. However, we have also conclusively demonstrated that during spontaneous offset, as opposed to onset, fade profiles are independent of the initial dose of relaxant administered. In these circumstances, therefore, there is a constant and reliable relationship between the absolute value of T1 and the T4 ratio. This observation implies that the use of specific endpoints to guide the use or otherwise of relaxant antagonists is likely to be safe for any specified relaxant.

Bowman has previously demonstrated (in cats) (16) the variable relationship between the degree of fade during onset and offset with vecuronium. He has suggested that the prejunctional receptors are isoreceptors of the postjunctional receptors with different pharmacologic profiles. If relaxants bind at different rates to these fade sites this would explain the observation that single twitch depression and fade develop and recover with different time courses. Our present results confirm these observations and previous findings in man using both vecuronium and atracurium (3).

When the two doses of relaxant used in the present study were compared during spontaneous offset as opposed to onset, we found that they appeared to have similar degrees of fade at all measured T1:control values. After a bolus dose of neuromuscular blocking drug, and after the redistribution phase lasting 4–5 half lives, the elimination phase of the drug begins when a pseudoequilibrium exists between the plasma and tissue concentration (19–21). It is a pseudoequilibrium because there is a slow transfer of drug from tissues to plasma, and elimination occurs, resulting in a slowly falling plasma level. Recovery from relaxants is determined essentially by plasma concentration. With the higher drug doses there is a more rapid initial decrease in plasma levels, but at the same T1 values for both groups, the plasma levels are similar. The suggestion that fade sites are isoreceptors of postsynaptic receptors explains the finding that, at similar T1 values, during recovery when the plasma levels

are changing slowly the T4 ratios are the same for both doses of vecuronium.

Because our study was concerned with the relationship between the value of T1 and the T4 ratio, results were included only if T1 after evoked reversal returned to within 10% of control values. Thirty-three patients were studied, but in only 22 were suitable results obtained. In the 11 rejected recordings T1 failed to reach 90% of control in 10, and in 1, T1 increased to values greater than 110% after reversal. Viby-Mogensen (22), in a recent review of the evoked electromyographic response, also noted that the response often did not return to 100% of control during recovery. It is presently not known whether this is due to technical problems such as changes in electrode impedance or position.

In conclusion, we have demonstrated that during onset of neuromuscular blockade a larger dose of vecuronium is associated with less fade than a smaller dose. During the onset of block there is, therefore, a variable and dose-related relationship between the height of T1 and the T4 ratio. Previously reported studies concerning the fade profile of relaxants that have been confined to onset of block must therefore be interpreted with caution. We have also shown that, with both doses, during recovery there is more TOF fade than during onset of blockade, and if the two doses are compared, at the same T1 values throughout recovery both doses have similar degrees of fade. Thus for bolus doses of vecuronium the T4 ratio during recovery bears a fixed relationship to initial T1 depression, although the dose may vary.

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Comparison of Hemodynamic Responses to Isoproterenol Infusion and Surgical Stress in Patients Given Cardioselective and Noncardioselective β-Adrenergic Antagonists

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DE BRUIJN N, REVES JG, CROUGHWELL N, KNOPES K. Comparison of hemodynamic responses to isoproterenol infusion and surgical stress in patients given cardioselective and noncardioselective β-adrenergic antagonists. Anesth Analg 1987;66:637–42.

Recent studies have demonstrated the presence of physiologically active β_2 receptors in the myocardium. We hypothesized that activation of cardiac β_2 receptors by endogenously released epinephrine and norepinephrine during surgical stress would add to the positive chronotropic response mediated by β_1 stimulation. Twenty patients scheduled for coronary artery bypass grafting were studied. Ten patients received a β_1-selective antagonist (atenolol, 6; metoprolol, 4) and ten patients received a nonselective β_1 and β_2 antagonist (propranolol) preoperatively. An isoproterenol dose–heart rate response test was performed. After stabilization, general anesthesia was induced followed by tracheal intubation and surgery. Hemodynamic data were recorded before induction, 1 min after induction, 5 min after intubation, 1 min before and after skin incision, 1 min before and after sternotomy. The ten patients on cardioselective β-blocker drugs had significantly greater increases in heart rate during isoproterenol administration than did the noncardioselectively blocked group of patients. Heart rate responses to tracheal intubation and surgical stress were not significantly different between the two groups at any point. We conclude that changes in heart rate during perioperative stress are primarily mediated through activation of β_1 receptors in the myocardium and that patients on either cardioselective or noncardioselective β-blockers have similar protection to adrenergic-mediated stressful hemodynamic events.

Key Words: HEART—β-adrenoceptor blockade. SYMPATHETIC NERVOUS SYSTEM—adrenergic blockade. ANESTHESIA—cardiovascular.

It has been generally accepted that β_1-adrenergic receptors are found in the myocardium and that the β_2-adrenergic receptors are located in the bronchial smooth muscle and the vasculature. However, evidence that cardiac β_2 receptors mediate positive chronotropic effects in man was reported by Brown et al. in 1983 (1). Recently Stene-Larsen et al., after examining a number of species, found that the distribution of β_2 receptors is related to the level of circulating epinephrine and that norepinephrine release from neurons can be facilitated by epinephrine acting on β_2 neuronal presynaptic membrane receptors (2). In man, a relatively high proportion of β_2 receptors are located on ventricular myocardial cells. Pharmacologic studies have indicated that these β_2 receptors are active and that stimulation of these receptors increases myocardial contractility (3). We hypothesized that activation of cardiac β_2 receptors by endogenously released epinephrine and norepinephrine during surgical stress would add to the positive chronotropic response mediated by β_1 stimulation. We examined this hypothesis by comparing perioperative heart rates in patients treated with either β_1 antagonists (cardioselective) or β_1 and β_2 antagonists (noncardioselective).

Methods

After institutional review board approval, 20 informed, consenting patients scheduled for elective coronary artery bypass surgery were entered into this protocol. All patients were receiving β-adrenergic antagonist drugs as part of their antianginal therapy. Doses had been adjusted to each patient's optimal clinical response. Ten patients received atenolol or metoprolol preoperatively (β_1-selective antagonists) and ten patients received preoperative propranolol (β_1 and β_2 antagonist). Each patient received the last oral dose of β antagonist within 3–4 hr (less than one drug half-life) of the study. Diazepam, 0.1 mg/kg or-

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ally, morphine sulfate, 0.1 mg/kg intramuscularly, and scopolamine, 0.2 mg intramuscularly, were given 1 hr prior to the study. Catheters were placed in a peripheral vein for drug and fluid administration and in the radial artery for continuous arterial pressure measurement, and an Oximetrix P7110 Opticath catheter was floated into the pulmonary artery for continuous monitoring of pulmonary artery pressure and mixed venous O_2 saturation.

After placement of monitoring catheters and after a 5-min stabilization interval, a standardized isoproterenol–heart rate (HR) response test was performed as previously described (4,5). The HR was calculated from ten consecutive R to R intervals at each measurement time. The HR was recorded at baseline and after 1, 2, 4, 8, and 16 μg intravenous bolus doses of isoproterenol. The heart rate was allowed to return to baseline after each dose of isoproterenol and the test was terminated if the HR increased more than 25 beats/min above baseline or if more than three premature ventricular contractions per minute were observed.

At the conclusion of the isoproterenol response test and after a 10-min period of stabilization, general anesthesia was induced with diazepam, 0.5 mg/kg IV, pancuronium, 0.1 mg/kg IV, 0.4% enflurane, and oxygen. Tracheal intubation was accomplished 4 min after induction. Hemodynamic data were recorded at baseline (B), 1 min after induction (I), 1 min after intubation (T), 5 min after intubation (T + 5), 1 min before skin incision (In − 1), 1 min after skin incision (In + 1), 1 min before sternotomy (S − 1) and 1 min after sternotomy (S + 1).

The hemodynamic variables were summarized as the mean ± SEM for each group. The patient demographic data, the dosages of various drugs received, and times associated with events of interest were compared between the two groups using the two-sample *t*-test. Comparisons of demographic data were made using the χ^2 test of proportions. Hemodynamic variables at each stage of measurement were tested for group differences using the two-sample *t*-test. Comparisons of mean hemodynamic measurements among stages within each group were made with a repeated measures analysis of variance (6).

The isoproterenol challenge data analysis required that a separate linear regression of percent change in HR versus isoproterenol dose (1, 2, 4, 8 or 16 μg) be computed by the method of least squares for each patient. The resulting slopes (in units of percent per microgram dose) were then correlated with various hemodynamic variables using Pearson correlation analysis (7). Differences were considered statistically significant if $P < 0.05$. To determine if the isoproterenol dose–response predicted HR change during the operation, a regression analysis was performed comparing the slope of the HR response to isoproterenol with the change in HR with intubation.

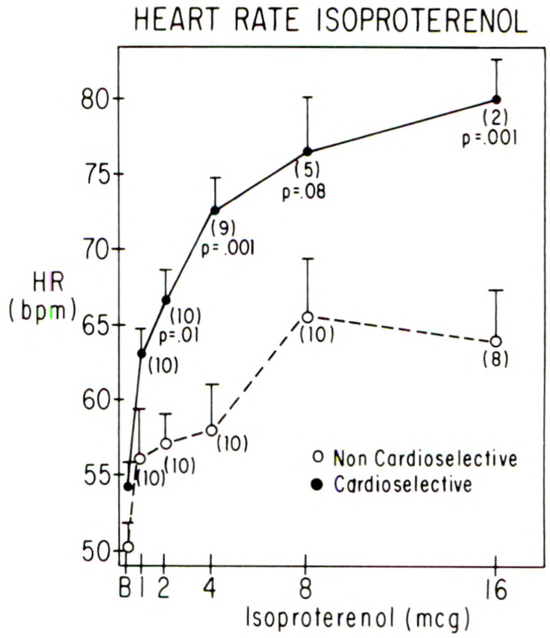

Figure 1. Heart rate after isoproterenol administration in patients medicated with cardioselective or noncardioselective β-adrenergic antagonists. The numbers in parenthesis indicate the numbers of patients in each group at each isoproterenol administration. An isoproterenol dose of 2 μg and higher caused a significantly higher HR response in patient on cardioselective β-adrenergic antagonists.

Results

There were no significant differences in patient age, weight, height, or body surface area (BSA) between the two groups. The mean ± SEM of the oral β-blocker doses were: propranolol, 161 ± 35 mg/24 hr; atenolol, 67 ± 11 mg/24 hr; metoprolol, 150 ± 29 mg/24 hr. The mean ± SEM heart rate response to isoproterenol of noncardioselective and cardioselective blocked patients is presented in Figure 1. The ten patients taking propranolol (noncardioselective) had significantly lesser heart rate responses to isoproterenol than did the atenolol (6) and metoprolol (4) (cardioselective) patients. Maximum HR was reached at lower doses of isoproterenol in the cardioselective group: thus there were fewer patients in the cardioselective group as the dose of isoproterenol increased. The slopes of the isoproterenol dose–HR change curves were significantly ($P = 0.01$) different. The dose–response curve of cardioselectively blocked patients was shifted to the left. The HR and blood pressure response to isoproterenol are presented in Table 1: the systolic (SBP),

Table 1. Hemodynamic Response to Isoproterenol

Dose (µg)		HR (beats/min) C	HR (beats/min) NC	SBP (mm Hg) C	SBP (mm Hg) NC	MBP (mm Hg) C	MBP (mm Hg) NC	DBP (mm Hg) C	DBP (mm Hg) NC
1	B	54 ± 3.6[a] (10)	50 ± 5.3 (9)	132 ± 18.1 (10)	139 ± 13.0 (9)	85 ± 10.1 (10)	86 ± 7.7 (9)	62 ± 11.4 (10)	60 ± 7.1 (9)
	A	63 ± 7.4 (10)	56 ± 9.3 (10)	131 ± 20 (10)	141 ± 14.0 (9)	82 ± 12.7 (10)	87 ± 7.8 (9)	57 ± 14.6 (10)	61 ± 7.3 (9)
2	B	54 ± 4.2[a] (10)	50 ± 5.2 (10)	131 ± 19.8 (10)	136 ± 15.5 (9)	82 ± 10.2 (10)	84 ± 8.7 (9)	58 ± 10.6 (10)	58 ± 7.5 (9)
	A	67 ± 6.4[a] (10)	57 ± 8.9 (10)	136 ± 19 (10)	139 ± 12.9 (9)	86 ± 11.6 (10)	86 ± 7.3 (9)	61 ± 13.7 (10)	59 ± 8.2 (9)
4	B	55 ± 4.6[a] (9)	50 ± 5.1 (10)	137 ± 18.2 (9)	136 ± 12.4 (9)	87 ± 9.4 (9)	84 ± 7.8 (9)	60 ± 11.7 (9)	57 ± 8.2 (9)
	A	72 ± 5.5[b] (9)	58 ± 9.8 (10)	141 ± 24.7 (9)	145 ± 14.4 (9)	85 ± 12.1 (9)	88 ± 6.1 (9)	57 ± 13.6 (9)	59 ± 7.4 (9)
8	B	54 ± 3.7 (5)	50 ± 5.3 (10)	132 ± 17.9 (5)	140 ± 16.1 (9)	87 ± 18.3 (5)	85 ± 6.9 (9)	65 ± 21.2 (5)	57 ± 5.8 (9)
	A	77 ± 7.2 (5)	65 ± 16.4 (10)	141 ± 25.5 (5)	148 ± 17.3 (9)	85 ± 18.8 (5)	87 ± 7.5 (9)	57 ± 17.7 (5)	56 ± 6.3 (9)
16	B	59 ± 6.4 (2)	50 ± 5.2 (8)	142 ± 19.1 (2)	141 ± 15.2 (7)	90 ± 14.1 (2)	85 ± 7.9 (7)	64 ± 11.3 (2)	57 ± 6.8 (7)
	A	80 ± 2.8[a] (2)	64 ± 11.4 (8)	137 ± 18.4 (2)	147 ± 20.1 (7)	74 ± 4.2 (2)	86 ± 11.2 (7)	42 ± 2.8 (2)	55 ± 9.4 (7)
32	B	(0)	47 ± 4.5 (6)	(0)	147 ± 13.3 (6)	(0)	87 ± 8.6 (6)	(0)	56 ± 9.4 (6)
	A	(0)	64 ± 12.9 (6)	(0)	167 ± 22.0 (6)	(0)	91 ± 7.9 (6)	(0)	53 ± 4.7 (6)

Abbreviations: B, baseline value; A, maximum response after isoproterenol; C, cardioselective β-blocked patients; NC, noncardioselective β-blocked patients. HR, heart rate; SBP, systolic blood pressure; MBP, mean blood pressure; DBP, diastolic blood pressure. Number of patients indicated in parentheses.
[a]$P < 0.05$.
[b]$P < 0.005$.

Table 2. Time Required for Heart Rate to Return to Baseline Levels after Isoproterenol

Isoproterenol dose (µg)	Time to return (sec) C	Time to return (sec) NC
1	82 ± 70 (10)	41 ± 33 (10)
2	137 ± 93 (9)	40 ± 25[a] (10)
4	155 ± 111 (5)	62 ± 34[b] (10)
8	244 ± 82 (2)	105 ± 65[b] (8)
16	—	177 ± 136 (6)

Abbreviations: C, cardioselective β-blocked patients; NC, noncardioselective β-blocked patients. Number of patients indicated in parentheses.
[a]$P < 0.05$.
[b]$P < 0.005$.

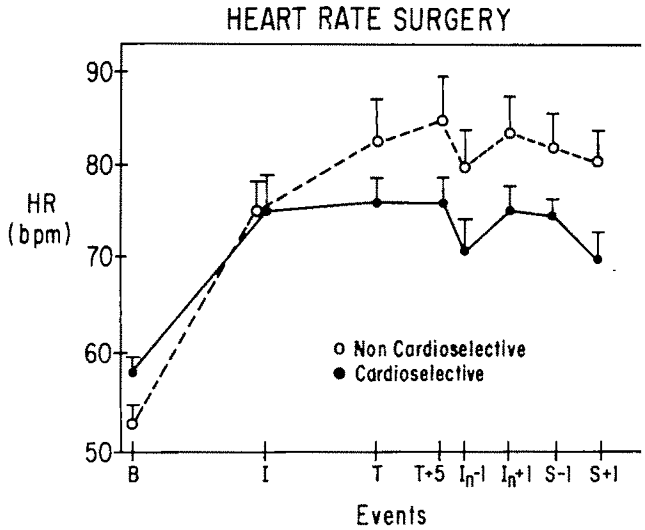

Figure 2. Heart rate during induction and surgery in patients medicated with cardioselective or noncardioselective β-adrenergic antagonists. B, baseline; I, 1 min after induction of anesthesia; T, 1 min after intubation; T + 5, 5 min after intubation; In − 1, 1 min before incision; In + 1, 1 min after incision; S − 1, 1 min before sternotomy; and S + 1, 1 min after sternotomy. At no time was there a statistically significant difference in HR response to surgical stimuli between the two groups.

mean (MBP), and diastolic (DBP) blood pressures were not significantly different in the two groups. There were significant differences in the time required to return to baseline after maximal HR was attained (Table 2). The patients on cardioselective β-adrenergic antagonist showed a significantly slower return to baseline than the patients on noncardioselective β blockers, an indication of a more intense isoproterenol effect in the former group.

Heart rate responses to tracheal intubation and surgical stress are depicted in Figure 2. Although there were changes from baseline, the HR responses were not significantly different between groups at any point. With the exception of baseline cardiac output (CO

Table 3. Hemodynamic Response during Anesthesia and Surgery

	Heart rate (beats/min)		Systolic blood pressure (mm Hg)		Diastolic blood pressure (mm Hg)	
	C	NC	C	NC	C	NC
Baseline	58 ± 6.5 (10)	53 ± 5.9 (10)	140 ± 17.7 (10)	144 ± 13.3 (10)	59 ± 7.0 (10)	63 ± 8.9 (10)
Induction +1	75 ± 8.1 (10)	75 ± 10.4 (10)	125 ± 19.2 (10)	127 ± 14.1 (10)	56 ± 7.4 (10)	59 ± 4.8 (10)
Intubation −1	69 ± 8.7 (10)	67 ± 9.6 (10)	120 ± 17.1 (10)	128 ± 20.2 (10)	53 ± 8.0 (10)	58 ± 6.6 (10)
Intubation +1	76 ± 9.6 (10)	83 ± 14.8 (9)	168 ± 26.7 (10)	170 ± 19.9 (9)	78 ± 11.1 (10)	79 ± 8.1 (9)
Intubation +5	76 ± 8.8 (10)	85 ± 16.1 (10)	159 ± 24.0 (10)	175 ± 21.6 (10)	71 ± 11.2 (10)	78 ± 10.6 (10)
Skin incision −1	71 ± 9.1 (10)	80 ± 13.3 (10)	143 ± 23.5 (10)	159 ± 19.1 (10)	69 ± 9.0 (10)	79 ± 12.5 (10)
Skin incision +1	75 ± 9.9 (10)	83 ± 13.8 (10)	182 ± 38.6 (10)	176 ± 21.2 (10)	93 ± 20.8 (10)	92 ± 15.4 (10)
Sternotomy −1	74 ± 7.1 (10)	82 ± 13.0 (10)	180 ± 32.6 (10)	171 ± 18.0 (10)	85 ± 14.6 (10)	86 ± 13.3 (10)
Sternotomy +1	70 ± 13.2 (10)	80 ± 13.1 (10)	153 ± 27.5 (10)	155 ± 25.7 (10)	78 ± 15.6 (10)	80 ± 15.7 (10)

Abbreviations: PAD, pulmonary artery diastolic pressure; SVR, systemic vascular resistance; C, cardioselective β-blocked patients; NC, noncardioselective β-blocked patients. Number of patients indicated in parentheses.
[a]$P < 0.05$.

and systemic vascular resistance (SVR), there was no significant difference between groups in hemodynamic variables during surgery (Table 3). There was a poor association between the change in heart rate with intubation and the slope of heart rate response to the isoproterenol test in both groups (noncardioselective blocked patients $R = 0.43$, $P = 0.25$; cardioselective blocked patients $R = 0.05$ and $P = 0.89$).

Discussion

Our results are consistent with those of other studies in that patients treated with combined β_1- and β_2-adrenergic antagonist drugs have greater attenuation of isoproterenol-induced HR response than patients treated with β_1 antagonists (8–11). Dagnino and Prys-Roberts (5) have shown the same effect in anesthetized patients. They demonstrated a large difference in CD_{25}, the dose of isoproterenol required to increase the HR by 25 beats/min between patients treated with cardioselective β-adrenergic antagonist and patients treated with noncardioselective β-adrenergic antagonists. Isoproterenol is a β_1 and β_2 agonist, and a greater HR response occurs in β_1-blocked (cardioselective) patients presumably because unblocked β_2 receptors in the heart mediate the positive chronotropic response to isoproterenol β_2 stimulation (1).

Our hypothesis that patients given β_1 antagonists could be vulnerable to β_2 stimulation by endogenous catecholamine release during the stress of anesthesia and surgery is confirmed by animal data (2) that provide evidence that the β_1 receptors found in the myocardium are functionally active. It has been postulated that patients treated with β_1 antagonists might be more susceptible to catecholamine release and that the stimulated, unblocked β_2 receptors in the heart would cause an increase in HR and contractility. We did not measure contractility in the study; however, the HR results are inconsistent with this hypothesis. In our data there is no evidence that HR or other hemodynamic variables reflect β_2 receptor activation during the stresses of anesthesia and surgery.

A potential problem in this study is that a purely β_1-selective β-blocker does not exist. All β-blockers are merely "semiselective". Cardioselectivity is a dose-related phenomenon; there is less cardioselectivity at higher doses. Thus our study design could not "prospectively" provide for equivalent doses of cardioselective and noncardioselective β-blockers. However, judging from the results the doses used were approximately equivalent because their effect was not significantly different during surgery.

The increase in HR observed in both groups above baseline levels 1 min after induction is probably due to the effect of pancuronium. The vagolytic effects of pancuronium are well known, and the consequences of the use of pancuronium in patients at risk to develop myocardial ischemia have recently been discussed by Savarese and Lowenstein (12).

The HR response to intraoperative events (Fig. 2) shows consistently higher heart rates in patients treated with noncardioselective β-adrenergic blockers. Although it might be argued that the lack of statistical difference is due to the limited number of subjects in the study, the fact that the significant difference in HR response to isoproterenol stimulation (NC < C) is actually reversed during the intraoperative events (NC > C) makes this unlikely.

The explanation for differences in HR response to isoproterenol and surgical stress response is that the endogenous catecholamines, epinephrine and norepinephrine, have different β agonist activities than

PAD (mm Hg)		Cardiac output		SVR	
C	NC	C	NC	C	NC
12 ± 2.6 (10)	13 ± 3.6 (10)	4.6 ± 1.0[a] (10)	3.9 ± 0.6 (10)	1430 ± 386[a] (10)	1770 ± 209 (9)
10 ± 3.5 (10)	12 ± 3.4 (10)	5.4 ± 1.3 (10)	5.0 ± 0.9 (9)	1149 ± 364 (10)	1262 ± 241 (9)
10 ± 2.7 (10)	11 ± 3.7 (10)	5.3 ± 1.5 (9)	4.7 ± 1.0 (9)	1089 ± 372 (9)	1356 ± 363 (9)
14 ± 3.2 (10)	15 ± 4.0 (9)	5.0 ± 1.3 (10)	5.1 ± 1.2 (9)	1720 ± 558 (10)	1688 ± 488 (8)
12 ± 3.2 (10)	13 ± 3.4 (10)	5.6 ± 1.7 (10)	5.1 ± 1.4 (9)	1434 ± 417 (10)	1720 ± 557 (9)
8 ± 2.9 (10)	10 ± 2.4 (10)	4.1 ± 0.8 (10)	4.4 ± 0.7 (9)	1754 ± 350 (10)	1874 ± 416 (9)
13 ± 7.8 (10)	13 ± 3.6 (10)	4.5 ± 1.0 (10)	4.3 ± 0.8 (10)	2070 ± 573 (9)	2293 ± 444 (10)
10 ± 4.9 (10)	12 ± 5.3 (10)	4.2 ± 0.7 (10)	4.7 ± 0.9 (9)	2207 ± 646 (10)	1946 ± 469 (9)
8 ± 3.7 (10)	10 ± 5.1 (10)	4.1 ± 0.8 (10)	4.0 ± 1.2 (9)	1977 ± 418 (10)	2105 ± 463 (9)

isoproterenol. Whereas isoproterenol stimulates β_1 and β_2 receptors, norepinephrine and epinephrine primarily activate β_1 receptors. At small doses epinephrine causes vasodilation (β_2 effect), whereas at larger doses there is an α_1 effect causing vasoconstriction. This may be inferred from studies of β-blocking drugs and hemodynamic response to epinephrine and norepinephrine infusion. Propranolol was not significantly different from metoprolol in blocking heart rate responses to norepinephrine infusions (11). Epinephrine infusion produced no significant difference in HR, SBP, or DBP in patients on either atenolol or pindolol (13).

Changes in heart rate during stress are mediated by the sympathetic nervous system. Norepinephrine plasma levels increase after the stimulus of tracheal intubation (14,15), and, because norepinephrine primarily stimulates β_1 receptors, cardioselective and noncardioselective β-blockers are equally effective in attenuating the response of HR to intubation. Although no control (non-β-blocked) patients were included in the present study, we have previously shown that β-blockade does attenuate the HR response to tracheal intubation (15). The predominant catecholamine response to surgical stress is epinephrine (16,17), which is generally considered more of a β_2 agonist than norepinephrine. In the present study during surgery, HR responses were equally blocked by both types of β-blockers.

Our observations that both types of β-blockers equally attenuate stress response to surgery is consistent with the results of exercise studies. Cardioselective and noncardioselective β antagonists equally block exercise-induced tachycardia (8,9). However, Perucca et al. demonstrated that 100 mg atenolol and 100 mg metoprolol were more effective than 40 mg propranolol in reducing heart rate response to exercise (10). Epinephrine and norepinephrine plasma levels increase with exercise, and we postulate that the reason that cardioselective and noncardioselective drugs are equally effective during exercise is the same as that discussed above for surgical stress.

The clinical implication of this investigation is that cardioselective and noncardioselective β-blockers provide similar protection to adrenergic-mediated, stressful hemodynamic events, but not to the administration of isoproterenol. We conclude that patients given either cardioselective or noncardioselective β-blocking drugs are equally protected against β-receptor agonist effects demonstrated in the heart during anesthesia and surgery-induced stress.

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Cadaver Anatomic Analysis of the Best Site for Chemical Lumbar Sympathectomy

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UMEDA S, ARAI T, HATANO Y, MORI K, HOSHINO K. Cadaver anatomic analysis of the best site for chemical lumbar sympathectomy. Anesth Analg 1987;66:643–6.

The lumbar sympathetic ganglia and their surroundings were examined anatomically in 19 human cadavers. The locations of the ganglia on the lumbar vertebral column at the level of the second and third lumbar vertebral bodies were analyzed statistically using a "ganglion score". The ganglia were most frequently found at the level of the lower third of the second lumbar vertebra, at the L2-3 interspace, and at the level of the upper third of the third lumbar vertebra on both the right and left sides. The points at which the sympathetic chain and the lumbar arteries crossed were at the middle third of the vertebral body in both the second and third lumbar vertebra. These results suggest that the most suitable point for placement of the tip of the needle used for chemical lumbar sympathectomy is not the midpoint of a vertebral body, but rather the lower third of the second vertebral body or the upper third of the third vertebral body.

Key Words: ANATOMY—lumbar sympathetic ganglion, lumbar artery. ANESTHETIC TECHNIQUES—lumbar sympathetic block.

The midpoint of the second and/or third lumbar vertebral bodies has been the recommended site for the needle point for lumbar sympathetic ganglion block since Bryce-Smith first described the method (1). However, lumbar sympathetic block is not always performed on the basis of quantitative anatomic analysis of the location of the ganglia. In clinical practice, the midpoints of lumbar vertebral bodies may not always be the best site for chemical sympathectomy because of variations in the location of the ganglia (2). Moreover, because of the lack of knowledge of the anatomic relationship between the ganglia and the lumbar arteries lumbar arterial vessels are sometimes punctured when the needle is advanced to the midpoint of lumbar vertebral bodies. For chemical sympathectomy performed under fluoroscopic control, it is important to establish the exact anatomic location of sympathetic ganglia and surrounding structures if the lumbar sympathetic block is to be an effective blockade and free of complications.

Using fluoroscopy in cadavers, the present study was undertaken to analyze quantitatively the anatomic relationships between lumbar sympathetic ganglia and second and third lumbar vertebral bodies. The relationship of the ganglia to lumbar arteries also studied.

Material and Methods

Nineteen cadavers were studied, 11 males and (males with a mean age of 70.2 ± 9.2 (± SD) yea death. Thirty-four sympathetic trunks (18 left an right) were studied after the exclusion of dama preparations.

After the removal of the abdominal and retro itoneal structures, the sympathetic trunks were posed. The sympathetic ganglia were recognize the thick portions in the paravertebral sympatl chain. Metal surgical clips (length 3.5 mm) were pl perpendicular to the long axis of the vertebral col at the cephalad and caudal borders of each gang found between the L-2 and L-3 vertebral bodies visualization of the sympathetic ganglia on x-ray fi Other surgical metal clips were diagonally place the lumbar arteries at the point at which they cro the sympathetic chain. The lumbar portion of the tebral column was then removed as a single bl which was x-rayed.

To determine the location of the lumbar syn thetic ganglia on the x-ray films, the lateral vie the vertebral column was divided into seven z (Fig. 1): zones 1, 2, and 3 were the upper, mic and lower thirds of the second vertebral body,

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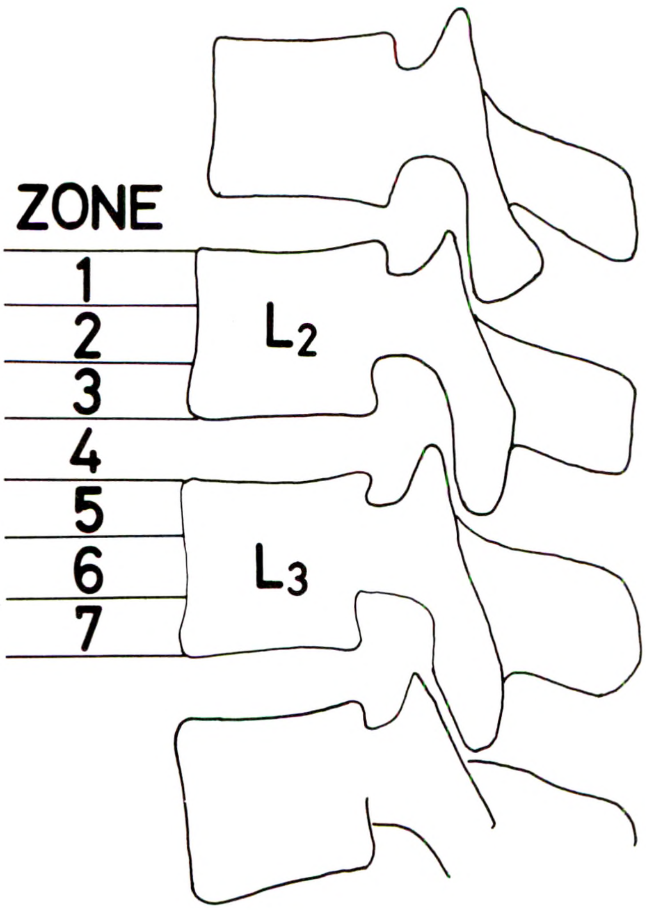

Figure 1. Schematic diagram of the lateral view of the lumbar vertebral column, depicting the seven zones. Zones 1, 2, and 3 are the upper, middle, and lower thirds of the second vertebral body, respectively; zones 5, 6, and 7 are the divisions of the third vertebral body; and zone 4 is the level of the intervertebral disk.

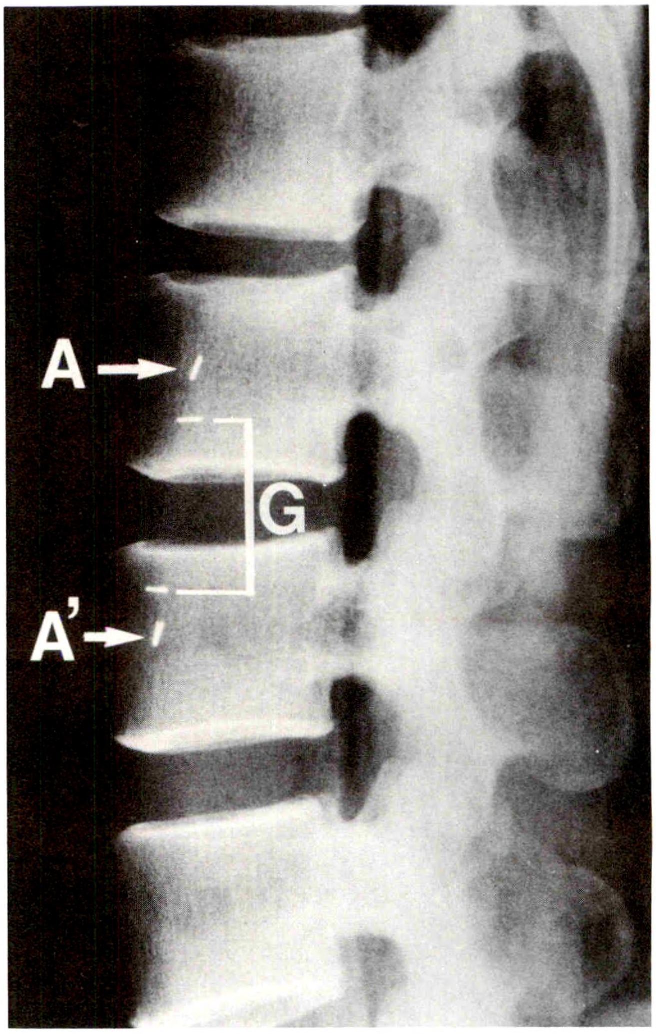

Figure 2. An x-ray film showing the lateral aspect of the lumbar vertebral column and the applied metal clips. The metal clips were applied under direct vision before the removal of the vertebral column as a single block. Diagonally placed clips show the points at which the sympathetic trunks cross the lumbar arteries at the second (A) and third (A') lumbar vertebral bodies. The horizontally placed clips were applied immediately above and immediately below the anatomic enlargement in the sympathetic chain, represented by "G," which indicates the location of the sympathetic ganglion.

spectively; zones 5, 6, and 7 were the upper, middle, and lower thirds of the third vertebral body; and zone 4 the portion of the L2-3 disc.

The ganglion score, which reflects the presence of ganglia in each zone was assigned as follows: 1 for absence of any ganglia in one zone; 2 for partial existence of some ganglia; and 3 for the existence of an entire ganglion, that is, one zone is fully occupied by the ganglion shown by metal clips.

Data were analyzed using Kruskal–Wallis one-way analysis of variance to determine statistical significance for each variable between any of the seven zones. Data were then analyzed nonparametrically using a Kruskal–Wallis test for statistical significance, that is, for validity in estimating the location of the ganglia.

The location of the points at which the sympathetic chain crossed lumbar arteries shown by radiopaque metal clips on x-ray lateral views was expressed as the distance from the lower border of each vertebral body as a percentage of the length of each vertebral body. From this, the 95% confidence limits of the localization of the crossing points was calculated.

Results

Figure 2 shows a typical lateral x-ray view. The location of the lumbar sympathetic ganglion is indicated by the midportion between the two surgical metal clips clamping the sympathetic chain. Points at which the sympathetic chain crossed lumbar arteries are in-

Table 1. The Mean ± SD Ganglion Score on Each Side

Side	Left (n = 18)	Right (n = 16)
Zone 1	1.22 ± 0.42	1.56 ± 0.79
Zone 2	1.72 ± 0.73	1.88 ± 0.86
Zone 3	2.11 ± 0.74	2.13 ± 0.70
Zone 4	2.39 ± 0.76	2.25 ± 0.83
Zone 5	2.39 ± 0.76	2.00 ± 0.87
Zone 6	1.78 ± 0.72	1.56 ± 0.79
Zone 7	1.17 ± 0.37	1.38 ± 0.78
Statistical analysis[a]	Z4 and Z5 > Z3 ($P < 0.01$) Z3 > Z2 and Z6 ($P < 0.001$) Z2 and Z6 > Z1 and Z7 ($P < 0.001$)	Z2, Z3, Z4, and Z5 > Z1 and Z6 ($P < 0.001$) Z1 and Z6 > Z7 ($P < 0.05$)

Abbreviation: Z, zone.
[a]Statistical analysis was made using Kruskal–Wallis rank test (see Methods).

Table 2. The Location of the Crossing Points of Sympathetic Trunks and Lumbar Arteries

	Second lumbar vertebra		Third lumbar vertebra	
	Left	Right	Left	Right
Location of crossing points[a]	47.3 ± 12.4% (n = 18)	47.1 ± 9.9% (n = 16)	49.1 ± 6.1% (n = 18)	48.2 ± 6.2% (n = 16)
95% confidence limits	41.2 ~ 53.4%	41.8 ~ 52.4%	44.8 ~ 53.4%	43.0 ~ 53.4%

[a]The crossing points are shown as the percentage of the distance from the lower border of each vertebral body to the whole length of each body. Data are means ± SD.

dicated by the metal clips clamping the arteries. In this instance, the large sympathetic ganglion extended from the lower third of the second vertebral body to the upper third of the third vertebral body, the ganglion scores thus being 1 point for zones 1, 2, 6, and 7; 2 points for zones 3 and 5; and 3 points for zone 4. The points at which the sympathetic chain and arteries crossed on the second and third vertebral bodies were situated in the middle third of each body.

Table 1 shows the mean value ± SD of the ganglion score in each zone on both sides. According to the statistical evaluation of the ganglion score, the location of the ganglia on the left side was most frequently in zones 4 and 5, and at least frequently in zones 1 and 7, whereas on the right side the ganglion was most often in zones 2, 3, 4, and 5, and least often in zone 7.

Table 2 shows the location of the crossing points of the sympathetic chain and lumbar arteries. The calculated 95% confidence limits of the location of the crossing points on each side of the vertebral bodies was in the middle third of each body.

Discussion

In lumbar sympathetic blockade, the tip of the needle need not necessarily be close to the ganglion when a large volume (8–12 ml) is injected, because the injected solution spreads along the sympathetic chain (3). However, the larger the amount of solution used, the more frequent are complications, including genitofemoral neuritis and lumbar neuralgia when neurolytic agents are injected (4). By placing the tip of the needle on the ganglion, lumbar sympathetic blockade can be performed with only a small amount of neurolytic solution and thus with little or no spread to adjacent structures. In fact, Cousins et al. have shown that injection of only 1.0 ml of a neurolytic solution completely bathes a ganglion (5). Therefore, knowledge of the exact location of the lumbar ganglia at L-2 and L-3 based on the ganglion score would be clinically valuable in lumbar sympathetic blocks in which only a small amount of a neurolytic substance is injected.

Our statistical analysis of the ganglion score indicated that the location of the sympathetic ganglion at L-2 and L-3 is most frequently at the level of the intervertebral disc on both sides. In patients undergoing surgical lumbar sympathectomy, the most constant ganglion, on both the right and left side, has been reported to be that near the second lumbar vertebra, usually on its lower third, but sometimes extending across the intervertebral space to the body of the third lumbar vertebra (6). These findings are consistent with our findings.

Lumbar vertebral arteries originate from the pos-

terior surface of the aorta and follow a dorsolateral course around the middle of the vertebral body (7). The anatomic situation of lumbar arteries means that they inevitably cross the sympathetic chain, which runs vertically on the vertebral column on the middle portion of each vertebral body. In our study, lumbar arteries crossed the sympathetic chain at the level of the middle third of each vertebral body (zones 2 and 6) in all cadavers. Recognition of the crossing point of the lumbar arteries and sympathetic chain is clinically important for avoiding arterial puncture; injury of these arteries may result in massive retroperitoneal bleeding (8,9), and injection of neurolytics into these arteries may cause neurologic sequelae (10,11).

Based upon our findings, the midportion of the lumbar vertebra (zones 2 and 6) is not suitable for placement of the tip of the needle during lumbar sympathetic block because this may result in arterial puncture. Although the level of the disc (zone 4) has the highest ganglion score, this site should also be excluded to avoid disc puncture. Zones 1 and 7 have a lower ganglion score than zones 3 and 5. Therefore, the lower third of the second vertebral body (zone 3) or the upper third of the third vertebral body (zone 5) are the most suitable levels at which to place the needle point. Although we have not performed a clinical study, these levels should be chosen as the target site for chemical sympathectomy using small amounts of neurolytics.

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Caudal Morphine for Postoperative Analgesia in Children:
A Comparison with Caudal Bupivacaine and Intravenous Morphine

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KRANE EJ, JACOBSON LE, LYNN AM, PARROT C, TYLER DC. Caudal morphine for postoperative analgesia in children: a comparison with caudal bupivacaine and intravenous morphine. Anesth Analg 1987;66:647–53.

We compared the efficacy, duration, and side effects of preservative-free morphine injected into the caudal space in children, with caudal bupivacaine and with intravenous morphine administration for relief of postoperative pain. Forty-six children, ages 1–16 yr, were randomly assigned to receive intravenous morphine (control group), caudal bupivacaine (0.25%, 1 ml/kg), or caudal morphine (0.5 mg/ml, 0.1 mg/kg). In half the patients given caudal morphine, the morphine was mixed with a dose of lidocaine adequate to produce sacral analgesia, to confirm correct caudal injection of the morphine. Caudal injections were performed at the end of surgery. Time until the first required postoperative intravenous morphine dose was recorded for each patient. The duration of analgesia was significantly greater with caudal morphine (median 12 hr, $P < 0.02$) than with caudal bupivacaine (median 5 hr), and both were greater than with intravenous morphine in control patients (median 45 min). Urinary retention, pruritis, and nausea appeared with slightly greater frequency in the caudal morphine group, but no delayed respiratory depression occurred. Caudal morphine (0.5 mg/ml, 0.1 mg/kg) provided 8–24 hr of analgesia in children without a significantly greater incidence of side effects than caudal bupivacaine or intravenous morphine.

Key Words: ANALGESICS, NARCOTICS—morphine. ANALGESIA—postoperative. ANESTHESIA—pediatrics. ANESTHETIC TECHNIQUES—caudal. ANESTHETICS, LOCAL—bupivacaine. PAIN—postoperative.

Orthopedic surgery and genitourinary surgery are often associated with appreciable postoperative pain in children. Although the management of acute postoperative pain has been the focus of many clinical studies in adults (1–3), less attention has been given to the management of pain in children, even though such pain is no less and is frequently undertreated (4,5).

Recently, the use of preservative-free morphine injected into the lumbar epidural or subarachnoid space has proven successful in children (6–8). However, correct placement of a lumbar epidural needle may be a difficult undertaking in a small child, and one study has shown a high incidence of accidental dural puncture (8). In contrast, caudal injection is a simple technique to perform in children, thus explaining the recent popularity of caudal injection of local anesthetics for operative anesthesia and postoperative analgesia in children (9–11). Inadvertent intravascular administration of local anesthetics during caudal injection in adults may be associated with convulsions or cardiovascular collapse, and the latter has recently been reported in a child (12). The use of preservative-free morphine might offer several advantages over the use of local anesthetics when administered into the caudal space. Among these advantages would be longer duration of effect, absence of motor and sympathetic block, and less severe consequences from accidental intravascular administration.

The epidural space in small children has spongy, gelatinous lobules and distinct spaces, as opposed to the densely packed fat lobules and fibrous strands that characterize the mature epidural space (13). This difference favors rapid longitudinal spread of drugs within the juvenile epidural space and may make caudally administered preservative-free morphine effective in treating postoperative pain in children. The purpose of this investigation was prospectively to

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Table 1. Pain Scores Used by Nurse Observers to Evaluate a Subject's Need for Supplemental Intravenous Morphine

1	2	3	4	5
Laughing, euphoric	Happy, contented, playful	Calm or asleep	Mild–moderate pain: crying, grimacing, restlessness; can distract with toy, food, parent	Severe pain: crying, screaming; inconsolable

evaluate the duration of postoperative analgesia and the incidence of side effects after caudal preservative-free morphine, compared with postoperative caudal bupivacaine and with intravenous morphine, using a double-blinded protocol and close, in-hospital observation.

Methods

Approval of our Institutional Review Board was obtained. After informed parental and (where appropriate to age) patient consent, 46 children, ages 1–16 yr, ASA physical status 1 or 2, and undergoing elective genitourinary or lower extremity orthopedic surgery, were randomly assigned to the control group, or to receive a postoperative caudal injection of either bupivacaine or preservative-free morphine, as described below. Preoperative or intraoperative narcotics were not administered to any patient. Halothane or isoflurane, with or without nitrous oxide, was used for operative anesthesia. In patients randomized to receive caudal injections, the injections were performed by one of the investigators at the conclusion of surgery, except for two patients receiving caudal morphine in whom injections were made before surgery because application of a spica cast followed surgery.

Caudal injections were made with the child in the lateral position with the hips and knees flexed. The skin over the coccyx and sacrum was cleansed with povidone–iodine solution and alcohol. After palpation of the sacral cornua, a 22- or 23-gauge needle was placed into the sacral hiatus, identifying the epidural space by loss of resistance as the needle passed through the sacral ligament. After failure to aspirate cerebrospinal fluid or blood, and a negative test dose in the bupivacaine group, the drug solution was injected. Patients were then extubated while deeply anesthetized and were taken to the postanesthesia recovery room while asleep. The patients, their families, and the nurses assessing pain were not aware of the treatment group assignment.

Treatment groups were as follows:

Intravenous Morphine Group (Control, $n = 15$): Children in this group did not receive caudal injections. Morphine sulfate, 0.05–0.2 mg/kg, was administered postoperatively every 2 hr as needed for analgesia.

Caudal Bupivacaine Group ($n = 15$): Children in this group received a postoperative caudal injection of 0.25% bupivacaine with 1:200,000 epinephrine, 1 ml/kg (maximum dose, 25 ml). Intravenous morphine was later given as described below.

Caudal Morphine Group ($n = 16$): Patients in this group were subdivided into two sections. Eight patients received postoperative caudal injection of preservative-free morphine alone (1 mg/ml diluted to 0.5 mg/ml with normal saline), in a dose of 0.1 mg/kg. In order to confirm proper placement of the injecting needle in the caudal epidural space, the remaining eight patients received postoperative caudal injection of preservative-free morphine, 1 mg/ml, in a dose of 0.1 mg/kg mixed with 1% lidocaine, 0.25 ml/kg. The lidocaine dose was calculated as being adequate to produce anesthesia in sacral dermatomes (10). Anesthesia in sacral dermatomes in the postanesthesia recovery room confirmed caudal injection. Intravenous morphine was given as described below.

For the first 24 hr after the operation each patient was monitored for respiratory depression with a chest wall impedance monitor to detect apnea, and with hourly determination of respiratory rates. Naloxone and resuscitation equipment were available at each bedside for 24 hr after surgery.

When awake in the recovery room, patients in the bupivacaine and morphine-plus-lidocaine groups were evaluated by an investigator for anesthesia to pinprick in sacral dermatomes. Two patients given caudal bupivacaine and one patient given caudal morphine-plus-lidocaine did not have a sensory block and were therefore excluded from the data analysis, thus reducing the sample sizes to 13 in the caudal bupivacaine group and 15 in the caudal morphine group.

The efficacy of postoperative analgesia induced by caudal bupivacaine and caudal morphine was compared with the efficacy of intravenous morphine (in

Table 2. Ages, Types of Operations, and Treatment Group Assignment of Experimental Subjects

	Age (yr)	Operation[a]	Duration of analgesia (hr)
Control group (intravenous morphine only)			
1	14	Bunionectomy	0.5
2	16	Osteotomy	0.7
3	5	Osteotomy	5.6
4	14	Osteotomy	0.8
5	2	Hypospadias	4.8
6	15	Tibial tumor excision	0.7
7	3	Osteotomy	1.5
8	1	Osteotomy	5.3
9	9	Osteotomy	0.2
10[b]	10	Hypospadias	>24
11	9	Osteotomy	0.5
12	3	Tenotomy	0.3
13	2	Osteotomy	0.5
14	13	Tibial tumor excision	0.8
15	1	Hypospadias	5.5
Mean	7.8		2.0
Median	—		0.8
Caudal bupivacaine group			
16[b]	3	Hypospadias	>24
17	5	Hypospadias	3.8
18	12	Osteotomy	9.8
19	2	Osteotomy	9.9
20	14	Osteotomy	4.5
21	2	Osteotomy	5.0
22	2	Hypospadias	3.9
23	10	Osteotomy	3.7
24	3	Osteotomy	10.0
25	5	Hypospadias	10.3
26	10	Osteotomy	11.0
27	2	Osteotomy	5.2
28	10	Open fracture reduction	3.5
Mean	6.2		6.7
Median	—		5.2
Caudal morphine group without lidocaine			
29	13	Osteotomy	20.5
30[b]	7	Hypospadias	>24
31	9	Tenotomy	9.7
32	1	Osteotomy	5.2
33	11	Osteotomy	4.0
34	1	Osteotomy	6.8
35	6	Osteotomy	12.1
36	16	Femoral bone graft	10.9
Mean	—		9.9
Median	—		10.3
With lidocaine			
37	2	Osteotomy	12.1
38	9	Femoral Bailey rods	15.7
39	4	Osteotomy	18.0
40	9	Femoral bone graft	16.6
41	5	Hypospadias	23.6
42	11	Femoral Bailey rods	4
43	12	Osteotomy	16.7
Mean	—		14.4
Median	—		16.6
Morphine group mean	7.7		12.6
Morphine group median	—		12.1

[a]Tenotomy denotes open adductor tenotomy; osteotomy denotes pelvic, femoral, tibial osteotomy or club foot repair with osteotomies.
[b]Patient excluded from calculation of mean duration of analgesia.

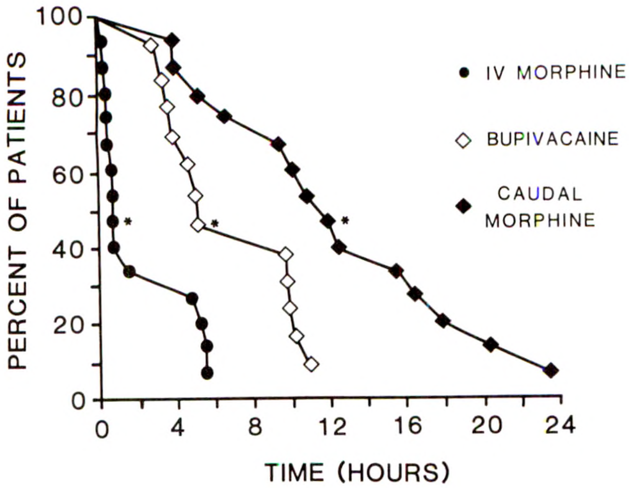

Figure 1. Percentage of patients in each group who did not require supplemental intravenous morphine during the 24-hr observation period. One patient in each group required no intravenous morphine; these three patients do not appear on the graph. The median times to first intravenous morphine dose for each experimental group are marked by an asterisk, which also denotes $P < 0.05$.

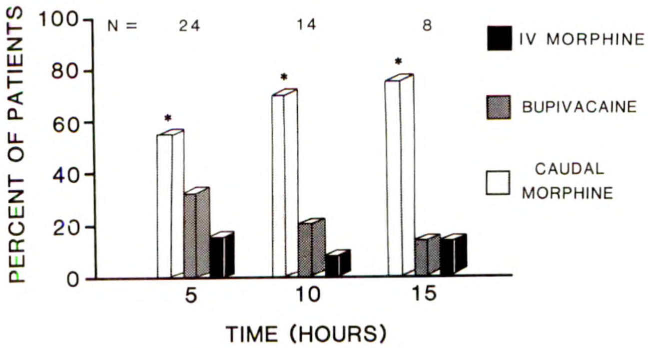

Figure 2. Proportion of patients from each group among those patients who did not require supplemental intravenous morphine 5, 10, and 15 hr after their operations. N indicates the total number of such patients with continuing analgesia at each time period; the asterisk denotes $P < 0.05$ for caudal morphine compared with the other groups (χ^2 test).

control subjects) by measuring the duration of time patients were pain-free after surgery, as reflected by the time before the first dose of supplemental parenteral narcotic was needed. In order to standardize criteria for the administration of the first and all subsequent doses of postoperative analgesics, nurses scored pain using a structured observation scale (Table 1) at 30-min intervals while in the recovery room, and every 2 hr thereafter for the first 24 hr after the operation. Intravenous morphine, 0.05 mg/kg, was administered for pain scores of 4 or 5, and repeated every 15 min as needed to achieve a score of less than 4. The time from admission to the postanesthesia recovery room until administration of the first dose of intravenous morphine was recorded for each patient, and cumulative morphine use was recorded for the first 24 hr after the operation. A log was kept at the bedside for noting the occurrence of possible complications, including respiratory depression, apnea, pruritis, urinary retention requiring bladder catheterization, or nausea and vomiting. Patients, their parents, and nurses were interviewed by one of the investigators after the 24-hr observation period to elicit subjective reactions to the control of postoperative pain.

The Kruskall–Wallis test and Mann–Whitney test with Bonferroni corrections were used for statistical comparison of the time to the first intravenous morphine dose. Comparisons of the incidence of side effects and of patient demographics were made by χ square tests with Bonferroni corrections. Least-square regression analysis was used to correlate duration of analgesia with patient age and weight. $P < 0.05$ was considered statistically significant.

Results

There were no differences in ages, types of operations, or anesthetic management of patients in each of the three groups (Table 2). Most patients underwent pelvic, femoral, or tibial osteotomies.

Efficacy

The median times to the first supplemental intravenous morphine dose were 45 min for the intravenous morphine group, 5 hr for the caudal bupivacaine group, and 12 hr for the caudal morphine group; differences between groups were statistically significant (Fig. 1).

Ten of 15 (67%) intravenous morphine (control) patients required morphine in the recovery room, and 14 (93%) received supplemental intravenous morphine within 6 hr after surgery. One patient in the control group did not require analgesics during the 24-hr observation period after hypospadias repair.

Of the 13 patients in the caudal bupivacaine group who had successful sacral block, all had cutaneous sensory blockade to the T4–10 level. Most experienced motor block of varying degree, ranging from paralysis to mild weakness of the lower extremities. All patients given epidural bupivacaine with demonstrable sensory blocks were analgesic upon awakening from general anesthesia: none required morphine while in the recovery room. Children who received bupivacaine blocks had pain scores of 1–3 for 3.5–10.5 hr; the majority (54%) of bupivacaine blocks receded by 6 hr. One patient in the bupivacaine group did not require analgesics during the 24-hr observation period after hypospadias repair.

Table 3. Frequency of Postoperative Complications in Each Group

	Intravenous morphine (n = 15)	Bupivacaine (n = 13)	Caudal morphine (n = 15)	χ^2	P
Respiratory depression	0	0	0	—	NS
Urinary retention	3	2	4	1.03	NS
Nausea/vomiting	5	4	7	1.36	NS
Pruritis	0	1	2	2.14	NS

Abbreviation: NS, no statistically significant difference.

In contrast, the range of duration of analgesia after caudal morphine was 4–24 hr. The onset of analgesia after caudal morphine was apparently rapid; upon awakening from general anesthesia, every patient in the caudal morphine group was analgesic, with pain scores of 1–3, and none required intravenous morphine in the recovery room. Indeed, only four of 15 (27%) caudal morphine patients required supplemental intravenous morphine within the first 8 hr after the operation: two of these patients received intravenous morphine after about 4 hr, neither of whom had confirmation of correct caudal placement by injection of lidocaine; a third patient had otalgia believed to be caused by operative use of nitrous oxide, and may have required morphine supplementation for this reason. Eleven patients who received caudal morphine (73%) maintained pain scores less than 4 for 9 to about 24 hr. One patient required no analgesics in the 24-hr observation period, also after hypospadias repair. After the first 4 postoperative hr, most patients who had not needed parenteral morphine were in the caudal morphine group (Fig. 2).

The duration of analgesia after caudal morphine did not correlate with the age or weight of the patients. There was a tendency for patients who received the mixture of preservative-free morphine with lidocaine to have a longer duration of analgesia than the patients who received preservative-free morphine alone (mean 14.4 and 9.9 hr, respectively), but this was not statistically significant (P = 0.22).

Patient and family acceptance of caudal morphine was enthusiastic. Among patients who had undergone operations of a similar nature previously, enthusiasm for the quality of analgesia provided by caudal morphine was especially high, even at the expense, in the instance of one 16-yr-old boy, of bladder catheterization. In contrast, many parents of children in the control group complained of inadequate analgesia during the first 24 hr after the operation.

Complications

There was no statistical difference in the frequency of complications among the three groups (Table 3). All patients who underwent hypospadias repair had routine postoperative bladder drainage. Among the other patients, intravenous morphine alone was associated with a 25% incidence of urinary retention requiring bladder catheterization (3/12 patients). Urinary retention was slightly more common in the caudal morphine group (4/13 patients, 31%), but two of these four patients received intravenous morphine prior to their inability to void. One patient given caudal bupivacaine required catheterization more than once. Nausea and vomiting were common in all groups, and occurred in the caudal morphine patients prior to the administration of intravenous morphine. Treatment with antiemetics was variably successful. Mild nasal pruritis occurred in two caudal morphine patients, but did not require treatment. Respiratory depression (respiratory rate less than 10/min) or apnea did not occur in any patient, although monitor false alarms were not uncommon.

Discussion

The caudal administration of 0.1 mg/kg of preservative-free morphine (with or without 1% lidocaine, 0.25 ml/kg) after lower extremity or genitourinary surgery was a safe and effective method of achieving prolonged postoperative analgesia in children. Caudal morphine provided approximately twice the duration of analgesia as caudal bupivacaine, without motor or sensory block. The onset of effect of caudal morphine in children was sufficiently rapid to provide analgesia in the recovery room a short time after the postoperative caudal injection, such that all the children who received caudal morphine were analgesic upon arousal from general anesthesia, which was within 15–20 min of the caudal injections in most instances. This is a notable departure from experience with adult patients, in whom the onset of analgesia after lumbar epidural morphine administration requires about 1 hr (14).

Lidocaine was added to the preservative-free morphine of half the caudal morphine group patients to confirm correct placement of the caudal needle by means of a short-acting drug that was not likely to

influence the outcome of the study. In so doing, we identified one failed injection in the group of eight morphine-plus-lidocaine patients. Although the addition of lidocaine to the caudal morphine injectate tended to increase the duration of postoperative analgesia, this increase did not reach statistical significance, and may have been a result of the inclusion of two patients in the group that received preservative-free morphine alone who may not have had true caudal injection of the study drug but in whom we did not have the ability to make that determination. Elimination of these patients from the comparison of those who received morphine alone vs those who received morphine with lidocaine further narrows the difference in mean durations of analgesia between those subgroups of subjects (13.9 and 14.4 hr, respectively).

We made no attempt to compare the quality of analgesia conferred by these three methods of controlling postoperative pain. Presently there are no validated and accepted tools for measuring pain in small children, and such a comparison must await the development of reliable pediatric pain scales. However, the subjective opinions of the hospital nursing staff who care for postoperative children and of our surgical colleagues, all of whom were blinded to treatment group assignment, were that there was no decrement in the quality of analgesia when comparing caudal morphine to bupivacaine, and that both were superior to control patients, in whom pain followed a cyclic pattern.

The frequency of side effects tended to be higher in caudal morphine patients, though a proportion of the side effects might have been attributable to subsequent administration of intravenous morphine. Though naloxone has been reported to be effective in treating urinary retention and nausea associated with epidural morphine (15,16), we did not evaluate this drug in our patients. We observed no cases of delayed respiratory depression, but our series is a small one. More experience with spinal narcotics in children will need to be gathered to assess fully the risk of respiratory depression after epidural morphine, to identify subpopulations at risk, to adequately inform families of risk, and to guide selection of appropriate drug dosage and monitoring technique. Until the full extent of such risk has been defined in children, respiratory monitoring should be used and equipment and drugs for resuscitation should be at hand.

Although it may be a laudable goal to eliminate postoperative pain in children, there are some instances in which pain is a valuable symptom that alerts the physician to the existence of a problem. During the course of this study, one orthopedic surgeon believed that the motor and sensory block associated with caudal bupivacaine delayed the recognition of a compartment syndrome in one patient who had undergone a tibial osteotomy, a recognized complication of this operation. After that experience, we chose not to administer caudal bupivacaine for postoperative analgesia after tibial osteotomies. It remains to be seen whether caudal morphine confers analgesia sufficient to blunt the intense pain of the tissue ischemia associated with compartment syndromes, but because caudal morphine does not ordinarily result in motor blockade, the loss of voluntary movement distal to a compartment syndrome should remain a diagnostic tool for the surgeon.

In 1981 Jensen (17) published the first and, to date, only report of caudal morphine for control of postoperative pain in children. In that study, caudal morphine (0.05 mg/kg) was compared to caudal bupivacaine (0.25%, 0.5 ml/kg) in young boys after outpatient circumcision or inpatient hypospadias repair. Only the inpatient group was evaluated for duration of analgesia. As in our experience, all patients except one with a failed block were analgesic in the recovery room. Jensen reported a duration of analgesia of 4–8.5 hr (mean 6 hr) after caudal bupivacaine in five children, and 5–37 hr (mean 20 hr) after caudal morphine in seven children. The incidence of nausea was similar in the two groups, but other side effects or complications were not studied. Unlike our study, a control group was not included, respiratory monitors were not used, nor is it specified how efficacy or duration of effect were determined. Therefore, our data confirm the results of Jensen, further demonstrate the efficacy of caudal morphine for analgesia after both genitourinary and orthopedic surgery in a wider age group, and demonstrate the absence of significant side effects compared to a control group receiving conventional parenteral narcotics.

In summary, caudal preservative-free morphine provided prolonged analgesia of longer duration than caudal bupivacaine and without side effects greater than those seen with conventional parenteral morphine, in children after lower extremity orthopedic and genitourinary surgery. Because a needle may be placed within the caudal space more easily than in the lumbar epidural space in children, and because of the present unavailability of appropriately sized epidural needles for pediatric use, caudal injections or caudal catheters may be the preferred route for administration of epidural narcotics in young children.

Duramorph provided by the A. H. Robins Company.

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Partition Coefficients for Sevoflurane in Human Blood, Saline, and Olive Oil

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STRUM DP, EGER EI. Partition coefficients for sevoflurane in human blood, saline, and olive oil. Anesth Analg 1987;66:654–6.

The purpose of this study was to determine partition coefficients for a new, rapid-acting inhaled anesthetic, sevoflurane. Blood samples were taken from 19 ASA physical status I–III patients ranging in age from 21 to 77 yr who were scheduled for elective surgery. At 37°C, we found a blood/gas partition coefficient of 0.686 ± 0.047 (mean ± SD), a saline/gas partition coefficient of 0.370 ± 0.016; and an oil/gas partition coefficient of 47.2 ± 2.7. These values are consistent with the clinical observation that sevoflurane is a potent inhaled anesthetic that produces a rapid induction of and recovery from anesthesia.

Key Words: ANESTHETICS, VOLATILE—sevoflurane. SOLUBILITY—sevoflurane.

Sevoflurane is a rapid-acting, potent, inhaled anesthetic (1,2) whose rapid uptake and elimination are due to a low blood/gas partition coefficient. Although the blood/gas partition coefficient was previously reported to be 0.60 (1), the methods by which this value for the coefficient were determined (including the number of samples analyzed and the effect of variables such as age or hemoglobin content) were not described. The purpose of this study is to verify in blood, saline, and oil the previous estimates of partition coefficients for sevoflurane. We will also determine the effect of age and hemoglobin concentration on the blood/gas partition coefficient.

Methods

With approval from our Committee on Human Research and consent from each patient, we obtained 30 ml of venous blood from each of 19 ASA physical status I–III patients ranging in age from 21 to 77 yr. The method of Lerman et al. (3) was used to determine the blood/gas and saline/gas partition coefficients of sevoflurane. Fifteen-milliliter samples of blood or 0.9% saline were placed in a 30-ml syringe and were equilibrated by tonometry with an equal volume of 2% sevoflurane for 2 hr in a waterbath at 37°C. The concentration of sevoflurane in the gas phase over each sample was determined by gas chromatography. The column was composed of 10% S.F. 96 on Chromasorb WHP, 68/80-mesh, 0.32 cm × 4.6 m maintained at 30°C. A nitrogen carrier stream flowing at 45 ml/min was delivered through the column to a flame ionization detector (at 200°C) which was supplied by hydrogen at 40 ml/min and air at 280 ml/min. An aliquot of the equilibrated blood or saline was transferred anaerobically to a 581-ml flask from which a portion of the air had been evacuated to produce a negative pressure. The negative pressure was used to draw the aliquot of blood or saline into the flask. Each flask was placed in a 37°C water bath and shaken every half hour for the ensuing 2 hr. When this procedure was completed, the sevoflurane concentration in the gas phase of the flask was determined by gas chromatography. The blood/gas partition coefficient (λ) was determined using the following equation:

$$\lambda = \frac{C_s(V_f/V_s)}{C_f - C_s}$$

where C_s is the concentration of sevoflurane in the gas phase in the 30-ml syringe used for tonometry, C_f is the concentration of sevoflurane in the gas phase of the flask, V_f is the volume of the flask, and V_s is the volume of the aliquot of blood or saline.

We sought to obtain dual determinations of the partition coefficient for each patient. However, in four patients the blood sample size was less than 30 ml, which precluded dual determinations. Data for one patient were deleted because the difference between

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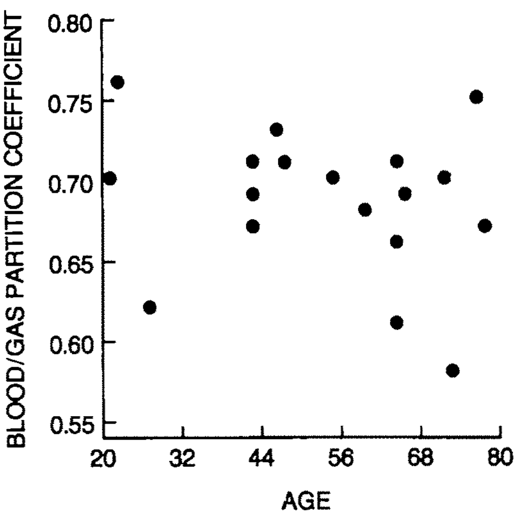

Figure 1. The blood/gas partition coefficient did not correlate with age ($r^2 = 0$). The regression equation was:

Partition Coefficient = 0.71 − 0.00051·Age.

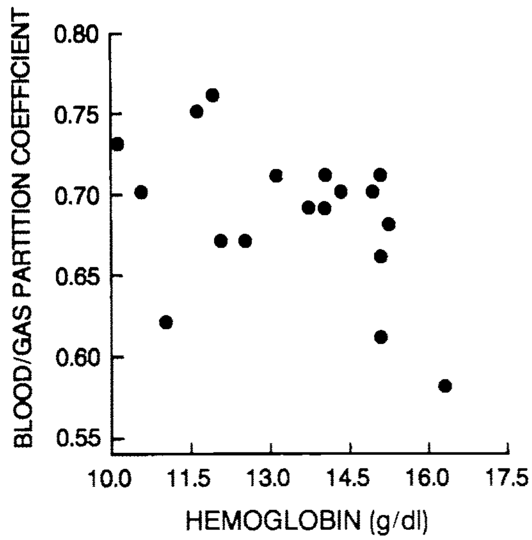

Figure 2. The blood/gas partition coefficient did not correlate with hemoglobin concentration ($r^2 = 0.12$). The regression equation was:

Partition Coefficient = 0.83 − 0.011·Hemoglobin.

the paired observations exceeded 16% of the mean value. The remaining paired values were averaged for each patient and the averaged value assumed to represent the partition coefficient for that patient's blood. This produced 18 values for the partition coefficient (14 paired and four unpaired). These values for the partition coefficient were regressed against patient age and hemoglobin concentration. We obtained five unpaired determinations of the saline/gas partition coefficient.

We made five unpaired determinations of the oil/gas partition coefficient for sevoflurane using the method described by Tanifuji et al. (4). Liquid sevoflurane (0.3 ml) was added to 100 ml of pure virgin olive oil and thoroughly mixed. Ten milliliters of this mixture was equilibrated by tonometry with 20 ml of air for 2 hr in a 30-ml syringe placed in a 37°C waterbath. The concentration of sevoflurane in the gas phase over the olive oil was then determined by gas chromatography. An aliquot (1.007 ml) of the equilibrated mixture was placed in a 581-ml flask and the flask sealed with a Teflon® stopper pierced with a needle to which we affixed a one-way stopcock. The flask was placed in a waterbath at 37°C. To increase the surface area for elution of sevoflurane from the oil phase, every half hour we rolled the flask to produce a film of the mixture on the wall of the flask. After 2 hr, the concentration of sevoflurane in the gas above the mixture in the flask was determined by gas chromatography. The equation used to calculate the oil/gas partition coefficient was that described earlier for blood and saline.

Results

Patients' ages averaged 53.5 ± 17.9 (mean ± SD) yr. Hemoglobin concentrations averaged 13.4 ± 1.8 g/dl. The blood/gas partition coefficient equaled 0.686 ± 0.047. The saline/gas partition coefficient averaged 0.370 ± 0.016. The oil/gas partition coefficient was 47.2 ± 2.7. There was no significant correlation ($P > 0.05$) between patient age or hemoglobin concentration and the blood/gas partition coefficient (Figs. 1 and 2).

Discussion

Our value of 0.686 ± 0.047 for the blood/gas partition coefficient for sevoflurane appears to be slightly higher than the value of 0.60 ± 0.07 published by Wallin (1) (attributed by Wallin to Harry Linde). Unfortunately, no mention is made in Wallin's article of the number of determinations of the partition coefficient and thus an accurate determination of the significance of this difference cannot be made. If we assume that Wallin (i.e., Linde) made at least five determinations, then the difference is statistically significant ($P < 0.05$, unpaired t-test). However, this difference is unlikely to have clinical significance; either value for the partition coefficient is consistent with an agent which provides a rapid induction of and recovery from anesthesia.

Neither patient age or hemoglobin concentration appeared to correlate with the blood/gas partition coefficient for sevoflurane. This finding contrasts with the results of previous studies demonstrating a small correlation of partition coefficient with both age (5)

and hemoglobin concentration (6). We speculate that our failure to find a correlation relates to the low solubility of sevoflurane in blood. There may be two explanations for this failure. First, as solubility approaches zero, the accuracy of measurement (as a percentage of the mean value) decreases and thus the signal-to-noise ratio increases. Second, as solubility approaches zero, any regression must have a zero slope.

Our saline/gas partition coefficient of 0.370 ± 0.016 is similar to the water/gas partition coefficient of 0.36 ± 0.01 reported by Wallin (1) (attributed to Linde). However, a water/gas partition coefficient usually is only 94.4% of the saline/gas partition coefficient (3). Applying this correction to Wallin's data gives a saline/gas partition coefficient of 0.34 ± 0.009. The difference between this value and our value is significant even if we assume that Wallin's sample size was only two.

Our oil/gas partition coefficient of 47.2 ± 2.7 is modestly lower than the value of 53.4 ± 1.2 given by Wallin (1) (attributed by Wallin to Munson). Either value for the oil/gas partition coefficient suggests an MAC for sevoflurane larger than the 2.5% observed for rats (7). Because MAC times the oil/gas partition coefficient equals a value of approximately 2 for most volatile anesthetics (7), an oil/gas partition coefficient of 50 would predict a MAC of over 4%. We have no explanation for this apparent disparity.

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Comparison of Atracurium and *d*-Tubocurarine for Prevention of Succinylcholine Myalgia

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SOSIS M, BROAD T, LARIJANI GE, MARR AT. Comparison of atracurium and *d*-tubocurarine for prevention of succinylcholine myalgia. Anesth Analg 1987;66:657–9.

We compared the incidence of postoperative myalgia (POM) and fasciculations when atracurium (ATR) or d-tubocurarine (DTC) was given prior to succinylcholine (SDC) for tracheal intubation in 44 ASA class I or II outpatient females undergoing laparoscopy. The subjects were assigned to one of three groups: group 1 received 0.025 mg/kg ATR; group 2 received 0.05 mg/kg DTC; and group 3 received saline (NS), all in a double-blind manner. Thiopental was administered 1 min and 45 sec after pretreatment in doses adequate to allow control of ventilation. Three minutes after pretreatment, SDC 1.5 mg/kg was given, and fasciculations were recorded on a scale of 0–3. All patients were questioned 1 and 3 days postoperatively about POM, using a scale of 0–3. Fasciculations occurred in 79% of patients given saline, in 46% of those receiving ATR, and in 12% of those given DTC. Eighty-five percent of ATR patients were free of POM on postoperative day 1. The corresponding figures for DTC and NS were 59% and 43%, respectively. Only the difference between ATR and NS achieved statistical significance. On the third postoperative day, POM was rare and there were no significant differences among the groups. We conclude that DTC is a better defasciculant than ATR. DTC was, however, not significantly better than NS in the prevention of POM. The findings suggest that ATR may be the drug choice for the prevention of POM.

Key Words: NEUROMUSCULAR RELAXANTS—succinylcholine.

Atracurium besylate (ATR), a new intermediate-acting nondepolarizing muscle relaxant, has been extensively investigated, but evaluations of its properties in attenuating postoperative myalgia (POM) after succinylcholine (SDC) have been conflicting and have not compared ATR with other agents commonly used for this purpose (1,2). The following study was designed to compare ATR and *d*-tubocurarine (DTC) given before SDC for tracheal intubation and to correlate the occurrence of POM and fasciculations in outpatients.

Methods

After approval by the Human Subjects Research Committee, 44 ASA class I or II girls and women aged 16–50 undergoing outpatient laparoscopy were selected. The patients were free from neuromuscular, hepatic, cardiovascular, and renal disease. None had anatomic abnormalities that might contribute to difficult tracheal intubation. The subjects were randomly assigned to one of three groups: group 1 ($n = 13$) received 0.025 mg/kg ATR, group 2 ($n = 17$) 0.05 mg/kg DTC, and group 3 ($n = 14$) saline (NS). The drugs were administered from syringes, all containing the same volumes, in a double-blind manner. Thiopental was administered 1 min and 45 sec after pretreatment in doses adequate to allow control of ventilation. The ulnar nerve was stimulated with impulses of 0.2 msec in duration and supramaximal amplitude at 1 Hz after induction, and the resultant thumb twitch was observed. Three minutes after pretreatment, SDC 1.5 mg/kg was administered and fasciculations were recorded on the following scale: nil [0]; mild fine fasciculations of the eyes, face, neck, or fingers without limb movement [1]; moderate fasciculations of greater intensity than mild that occurred at more than two sites or that produced limb movement [2]; severe vigorous, sustained, and widespread fasciculations possibly requiring forceful retention [3].

All patients were contacted 1 and 3 days postoperatively by an investigator blind to the drugs given.

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Table 1. Fasciculations

	Nil (%)	Mild (%)	Moderate (%)
ATR	54[a]	31	15
DTC	88[a,b]	6	6[b]
NS	21[b]	36	43[b]

Abbreviations: ATR, atracurium; DTC, *d*-tubocurarine; NS, Saline.
[a] $P < 0.05$ between ATR and DTC.
[b] $P < 0.05$ between DTC and NS.

Table 2. Myalgia on Postoperative Day 1

	Nil (%)	Mild (%)	Moderate (%)
ATR	85[a]	15	0
DTC	59	35	6
NS	43[a]	43	14

Abbreviations: ATR, atracurium; DTC, *d*-tubocurarine; NS, saline.
[a] $P < 0.05$ between ATR and NS.

They were questioned about POM, and the answers scored as follows: absence of pain other than characteristic postlaparoscopic gas pains (3–5) [0]; mild muscle stiffness or pains, when specifically asked about, in the nape of the neck, or in the shoulders and lower chest on deep breathing [1]; moderate muscle stiffness and pains spontaneously complained of by the patient that required analgesics [2]; severe, incapacitating generalized muscle stiffness or pain [3]. Multivariate analysis of variance followed by Duncan's multiple-range test and Fisher's exact probability test were performed to detect any statistically significant difference in dependent variables among the groups. Levels of $P < 0.05$ were considered statistically significant. All results are expressed as a mean ($\pm$SD).

Results

There were no significant differences among the groups in terms of age or weight. Relaxation was adequate for intubation in all cases. All patients were discharged from the hospital on the day of surgery. The results are summarized in Tables 1–3.

Violent fasciculations were not seen in any patients. After ATR, 31% of the patients had mild and 15% had moderate fasciculations. Fasciculations were mild in 6% and moderate in 6% of patients after DTC and mild in 36% and moderate in 43% of patients given NS.

Severe POM was not experienced by any patient. On postoperative day 1, the only myalgia in ATR patients was mild, occurring in 15%. POM was mild in 35% and moderate in 6% of DTC patients. The corresponding results for NS were 43% and 14%, respectively. Significantly more ATR patients (85%) than NS patients (43%) were free of POM. There was no significant difference between ATR and DTC or between DTC and NS in this regard. On the third postoperative day, POM was rare and there were no significant differences among the groups.

Of the six ATR patients who had fasciculations, only one had myalgia on postoperative day 1. After DTC, two patients had fasciculations but neither had POM on day 1. After NS, 11 patients had fasciculations but only five of these had POM on postoperative day 1.

Of the seven patients given ATR who had no fasciculations, one had POM on day 1. Of the 15 patients given DTC who had no fasciculations, seven had POM on day 1. After NS, three patients had no fasciculations but all them had POM on postoperative day 1.

Discussion

Brodsky and Ehrenwerth (6) and Craig (7) have stressed the need for standardization of such factors as the age and sex of the patients studied, the type of operation, the patients' positions during surgery, whether the patients are ambulatory, and the method of questioning the patients in assessing POM. Churchill-Davidson (8) and others (9,10) have noted that POM is more common in ambulatory patients. Newman and Loudon (11) and others (12) found POM to be more common in females. Our investigation is consistent with these findings.

A 3-min interval was chosen in our study for the time between the defasciculant and the SDC since Horrow and Lambert (13) and Takki et al. (14) have shown this to be the optimal interval for DTC to prevent fasciculations and POM. The doses of ATR and DTC used in this study are 10% of their ED_{95} (15,16).

Manchikanti et al. (2) studied ATR 0.05 mg/kg as pretreatment for SDC in outpatients of both sexes undergoing arthroscopy. Eighty-five percent of the patients in their control group had fasciculations after SDC 1.5 mg/kg. This is close to our 79% figure. Only 35% of the patients in the study of Manchikanti et al. who were given ATR 0.05 mg/kg prior to SDC 1.5 mg/kg had fasciculations. This compares to 46% of our patients who received ATR 0.025 mg/kg. Similarly, POM was seen in 45% of Manchikanti's control group and in 10% of his ATR group. Our corresponding figures are 57% and 15%, respectively.

Budd et al. (1) studied ATR 2.5 mg (0.04 mg/kg) and 5 mg (0.08 mg/kg) given prior to SDC 1 mg/kg in a study of inpatients undergoing oral surgery. Both

Table 3. Fasciculations and Postoperative Myalgia in Patients Receiving ATR, DTC, or NS prior to Succinylcholine

	Pain		No pain
ATR	0 F		F F F F F 0 0 0 0 0 0
DTC	0 0 0 0 0 0 0		F F 0 0 0 0 0 0 0 0
NS	0 0 0 F F F F F		F F F F F F
Number of patients			
10	5	0	5 10

F denotes patients fasciculating; 0 denotes patients having no fasciculations.

Abbreviations: ATR, atracurium; DTC, *d*-tubocurarine; NS, saline.

groups had significantly less fasciculation than did control patients, but there was no significant difference in POM with ATR in either dose when compared with controls.

Our study shows that POM is more common on the first than on the third postoperative day. This is consistent with the reports of Parbrook and Pierce (17) and others (9).

We confirm the observation that there is no strong correlation between fasciculations and POM (18,19). While demonstrating that DTC is an excellent defasciculant, we were initially surprised that it was not significantly better than NS for preventing POM since DTC pretreatment is widely advocated. This differs from other reports in which inpatients were studied (14,19). It is, however, consistent with a study by Bennetts and Khalil (20) that included some outpatients and the studies by Perry and Wetchler (21) and Fahmy et al. (22) in ambulatory patients.

In summary, our study is the first to compare ATR with DTC for use prior to SDC. The results show that although ATR is significantly better than NS for the prevention of fasciculations, DTC is better than ATR. DTC was, however, not significantly better than NS in preventing POM. The findings suggest that ATR may be the drug of choice for the prevention of POM.

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Technical Communication

A Laboratory Evaluation of Resistive Intravenous Flow Regulators

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Accurate and reliable administration of potent cardiotonic and vasoactive medications by constant infusion is a necessary part of quality anesthesia care. Several techniques are available for providing constant drug infusion: peristaltic fluid pumps, syringe fluid pumps, gravity-driven flow controller pumps, passive resistive flow regulators, and standard roller clamp infusion sets. Pumps are bulky, expensive, and require electric power. On the other hand, the standard roller clamp is notoriously unreliable (1–6). The remaining alternative, a resistive flow regulator placed in series with a standard infusion set, usually offers more precise control of fluid path resistance than is available with roller clamps (7). These relatively inexpensive devices do not require electric power. However, in the absence of active (energy-requiring) flow control, the net force for fluid flow becomes the difference between gravity (bag height) and catheter, venous, and cardiac factors (back pressure). Simple hydraulic physics indicates that flow rate should be linearly dependent on the back pressure, a most undesirable feature. Despite this shortcoming, these devices are commonly used to regulate many infusions, including those for potent medications; in the United States, annual sales exceed several million units (manufacturers' representatives, personal communication).

Of several brands currently available, some feature a metered dial, implying that a desired flow rate can be selected with reasonable accuracy. Our clinical experience with one such device led us to investigate the performance of four types of resistive regulators in the laboratory. Our tests were based on the following criteria for an ideal resistive regulator: 1) for those with a metered dial, accurate delivery with minimal variation of flow rate among units; 2) a flow rate independent of changes in the back pressure distal to the regulator; and 3) ability to make small changes in flow rate with reasonable ease.

Methods

This in vitro study of resistive intravenous regulator performance modeled several clinical circumstances. We tested four brands of currently marketed regulators: Dial-A-Flo (DAF), catalog no. 1671, Abbott Laboratories, North Chicago, IL; Stat Master (SM), catalog no. S-100-12, Master Medical Corporation, Phoenix, AZ; CorrectFlo (CFLO), Biomedical Dynamics Corp., Minneapolis, MN; and Arm-A-Flow (AAF), Armour Pharmaceutical Company, Kankakee, IL.

Experiment 1 evaluated regulator accuracy in the two brands, DAF and SM, that have a metered dial. Five units of each brand were selected. A minidrip infusion set (catalog no. 2C002, Travenol Laboratories, Deerfield, IL) was attached to a 250-ml bag of 5% dextrose in water (catalog no. 2B0062, Travenol Laboratories). The regulator was affixed to the distal end of the infusion set, and an 18-gauge 44-mm-long catheter (Jelco, catalog no. 4054, Critikon, Tampa, FL) was attached distal to the regulator tubing. Fluid exited the catheter to a graduated cylinder (10 ml with 0.1-ml graduations or 50 ml with 1.0-ml graduations). Printed instructions accompanying the DAF recommend placing the middle of the fluid bag 30 inches above the tip of the catheter. This recommendation was followed for all DAF and SM units.

The ten regulators were evaluated sequentially, each at a low flow setting (30 ml/hr for DAF, 10 ml/hr for SM) and a high flow setting (100 ml/hr for both DAF and SM). The chosen rates correspond to printed set-

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tings on each unit. At each setting, volume delivered was measured over 20 min and expressed as an hourly rate. During this time, the number of drops formed over 1 min were counted during the first, fifth, tenth, 15th, and 19th min. Drops were counted visually with the aid of a hand-held toggle switch counting device. Fluid levels in the bags were restored to their original heights at the end of each 20-min measurement. Deviation from expected flow was calculated as (actual − expected) × 100/expected. Thus the larger the deviation, the poorer was the accuracy.

In order to compare flow rates among individual DAFs or SMs, some measure of the inherent variability of a unit ("within variance") is needed. Drop count data provided this measure. The drop count data were analyzed by one-way analysis of variance (ANOVA). The five drop counts for each of the ten units at a given setting were considered replications. This assumes no time-dependent change in drop count over the 20-min observation period. Plots of drop count versus time confirmed this assumption. Variability among the five DAFs or the five SMs was evaluated using ANOVA to test for an effect of DAF or SM unit on drop count.

Experiment 2 was designed to test the effect of increased back pressure generated by a large carrier flow (CF) and by catheter constriction. All four brands of regulator were tested. The regulator fluid path and the CF fluid path were joined at a low-resistance manifold (Fig. 1). A manometer attached to the manifold measured the pressure where the fluid paths converged. Fluid passed through the manifold on a level surface through the 18-gauge catheter to atmosphere. Three units of each brand were tested sequentially at the 100 ml/min setting. Each time, with neither CF nor catheter applied, the minidrip infusion set was calibrated by counting drops formed over 10 min and dividing that number into the volume delivered during that time, yielding drop size. Drop count per minute did not change in a consistent manner over the 10-min period.

For each of the 12 units, seven conditions of varying back pressure were studied: 1) no catheter or CF; 2) with catheter only; 3) catheter plus CF = 2 ml/min; 4) catheter plus CF = 4 ml/min; 5) catheter plus CF = 10 ml/min; 6) CF = 10 ml/min and a loose extrinsic clamp applied to the catheter; and 7) CF = 10 ml/min and a tighter extrinsic clamp applied to the catheter. For each study condition, the DAF or SM metered dial was first set to 100 ml/hr; since CFLO and AAF have no metered dial, a 100-ml/hr flow rate was approximated by adjusting each regulator to obtain 100 drops/min. Then the CF was begun and a clamp applied, if indicated. The CF rates were approximate

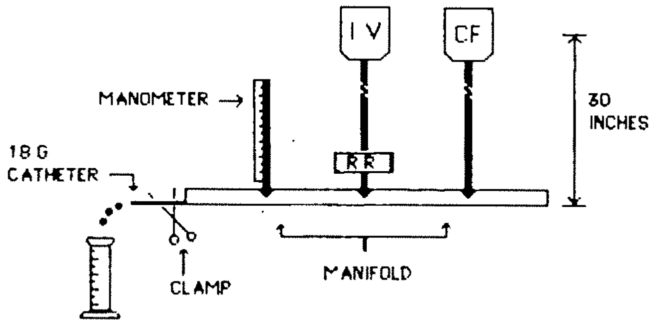

Figure 1. Arrangement of materials for measuring effect of various conditions on back pressure and flow rate. Carrier flow (CF) from a 1000-ml bag of fluid enters a manifold via a large drop administration set. The controlled flow (IV) enters the manifold via a minidrip administration set in series with the regulator (RR). A manometer attached to the manifold measures pressure between the junction of flow and the 18-g catheter. Clamps were applied to the catheter.

and assumed that 15 large drops formed 1 ml of fluid. The infusions were run for 10 min. Drops formed over 2 min were counted for the first and last 2-min periods of the infusion. Since no pair of drop counts differed by more than 5%, the mean value of each drop count pair was used in calculations. Using the calculated volume per drop, volume delivered by each regulator over 10 min was calculated and expressed as ml/hr. Back pressure was measured as the height of the fluid column in the manometer. For the conditions requiring a clamp, the clamp was applied to each regulator so that the resultant back pressure would equal 20.5 cm water for the loose clamp and 28.5 cm water for the tighter clamp. In this way, the effect of a known back pressure on regulator delivery rate would be tested, as opposed to the variable effect of a clamp on back pressure. The relationship between volume delivered and back pressure was analyzed using least squares regression and tested for significance with Student's *t*-test.

Ease of setting and changing flow rates were evaluated subjectively by one investigator (JRJ) during the course of conducting the experiments.

Results

In experiment 1 the DAF delivered 22.5 ± 2.16 ml/hr (mean ± SD) at the 30 ml/hr setting, yielding a deviation of −25.1 ± 7.2%. Flow rate at the 100 ml/hr setting was 76.5 ± 3.52 ml/hr, corresponding to a −23.4 ± 3.5% deviation. The SM flow rate at the 10 ml/hr setting was 9.99 ± 2.52 ml, for a deviation of −0.10 ± 25.2%. At the 100 ml/hr setting, the flow rate was 95.8 ± 12.5 ml/hr, yielding a −4.08 ± 12.5% deviation. Table 1 displays these results. ANOVA re-

Table 1. Flow Rates in the Accuracy Experiment

DAF unit	30 ml/hr setting Flow (ml/hr)	30 ml/hr setting % deviation	100 ml/hr setting Flow (ml/hr)	100 ml/hr setting % deviation
1	20.6	−31.5	73.5	−26.5
2	25.5	−15.0	81.0	−19.0
3	21.3	−29.0	75.0	−25.0
4	24.0	−20.0	79.5	−20.5
5	21.0	−30.0	73.5	−26.5
Mean	22.5	−25.1	76.5	−23.5
SD	2.16	7.21	3.52	3.52
SM unit	**10 ml/hr setting Flow (ml/hr)**	**10 ml/hr setting % deviation**	**100 ml/hr setting Flow (ml/hr)**	**100 ml/hr setting % deviation**
1	12.3	23.0	78.0	−21.9
2	11.9	18.5	104.	3.60
3	10.5	5.00	87.6	−12.3
4	6.00	−40.0	103.	3.00
5	9.30	−7.00	107.	7.21
Mean	9.99	−0.10	95.8	−4.08
SD	2.52	25.2	12.5	12.5

vealed a strong effect of DAF unit on drop count data for both the 30 ml/hr setting (calculated $F_{4,20} = 33.13$, $P << 0.01$) and the 100 ml/hr setting (calculated $F_{4,20} = 29.72$, $P << 0.01$). A similarly strong effect of SM unit on drop count data was also revealed at both the 10 ml/hr setting ($F_{4,20} = 220$, $P << 0.01$) and the 100 ml/hr setting ($F_{4,20} = 230$, $P << 0.01$).

Figure 2 displays the effects of the seven conditions on back pressure and flow rate for each of the regulators. DAF, SM, and CFLO flow rates varied inversely with back pressure. Scatter plots of flow rate versus back pressure (Fig. 3) show linearity for the DAF ($r^2 = 0.82$), SM ($r^2 = 0.83$), and CFLO ($r^2 = 0.88$). For each regression $P << 0.001$.

As Figure 3 indicates, the AAF does not decrease flow rate with increasing back pressure. In fact, it overcompensates: flow rate slightly increases with increasing back pressure ($r^2 = 0.23$, $P = 0.03$). Flow rate rises by 1 ml/hr (1%) for each 10 cm H_2O rise in back pressure. Although statistically significant, the correlation coefficient is poor. Furthermore, this relationship has no clinical importance.

The four brands differed greatly in the ease with which flow rates could be set and changed. The screw-type mechanism on the CFLO proved to be the one most easily manipulated. The DAF and SM, though more difficult to set than the CFLO, could still be manipulated with sufficient ease to satisfy clinical needs. In contradistinction, the AAF is difficult to use. Flow settings are accomplished by turning a rotary cap while simultaneously pushing on it. The force needed to depress the cap is excessive; it is similar to that needed to open a child-resistant medication cap. Moreover, while applying this force, it is difficult to make fine adjustments.

Discussion

Resistive flow regulators offer several advantages over roller clamps: elimination of cold flow, or creep, and fine control of fluid path resistance. Cold flow, a property of soft plastics, changes the shape of the tubing fluid channel over a period of 1 hr after a roller clamp is positioned (2–4). These geometrical changes decrease flow, yielding a flow rate decrement of about 38% 5 min later and of 60 ± 21.2% 60 min later (4). "Even-flow" roller clamps can limit (4), but not eliminate (6), the effect of cold flow. Resistive regulators eliminate cold flow by employing metering channels composed of materials not subject to cold flow. The second advantage of resistive flow regulators is a control of fluid path resistance that is finer than that attainable with various roller clamps. Tapered or helical fluid paths provide this control. The ability to alter resistance in small gradations (precision), however, does not necessarily imply accuracy of markings on the metered dial.

Compared with fluid pumps, resistive regulators are considerably cheaper and easier to set up. However, unlike pumps, many brands of resistive regulators fail to compensate for several factors that affect flow rate, such as a decreasing fluid level in the bottle or bag, a change in venous back pressure at the infusion site, or a change in venous resistance leading from infusion site to the heart (2,5). The adverse effect these variables can have on accuracy and stability is often a more important consideration than cost.

Some of these factors have been previously studied, such as the variation of venous pressure and venous resistance with time and with patient motion (2,6). In several patients whose infusions had stopped, flow was restored by stroking or patting the veins (2). Increased resistance in catheters also occurs. In one study, five of 11 infusions that stopped flowing spontaneously had clotted catheters (2). Thus, changes in resistance or venous pressure are well-documented clinical occurrences.

Neither the DAF nor the SM proved acceptable in the accuracy experiment. For the DAF, deviations ranging from −15.0 to −31.5% occurred. These results compare to those of Rithalia and Rozkovec (8). Those investigators, who studied only the DAF, found a slightly better but highly variable flow rate deviation (10 ± 10%) compared with −25.1 ± 7.21% in the current study. The SM performance was equally poor. While the means of the deviations of the five SMs tested were small (−0.1% at 10 ml/hr and −4.1% at

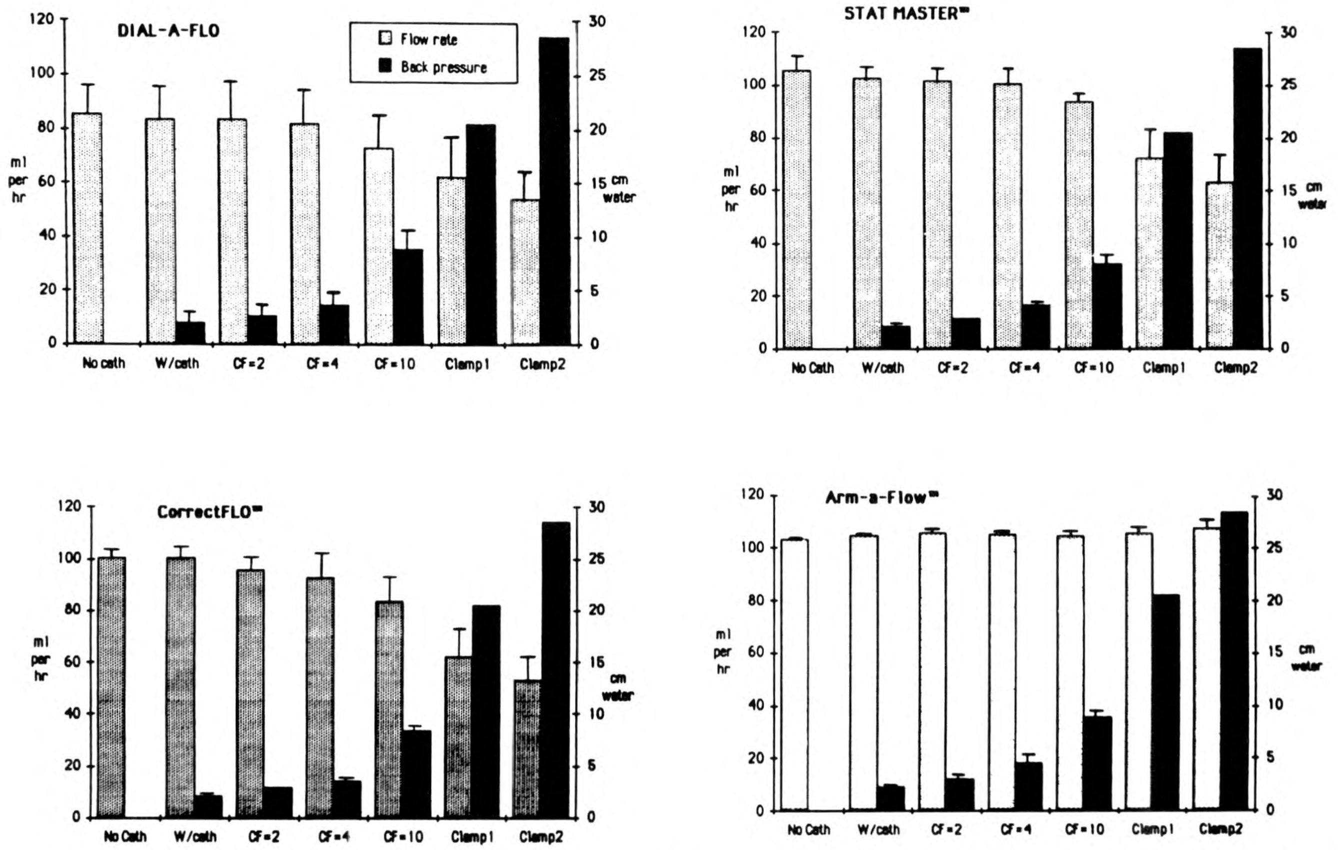

Figure 2. Results of the second experiment. The seven conditions that appear on the horizontal axis are: No cath, neither 18-g catheter nor carrier flow (CF); W/cath, with catheter and no CF; CF = 2, with catheter and CF of 2 ml/min; CF = 4, with catheter and CF of 4 ml/min; CF = 10, with catheter and CF of 10 ml/min; Clamp1, with catheter, CF of 10 ml/min, and a clamp applied loosely to the catheter; and Clamp2, with catheter, CF of 10 ml/min, and a clamp applied more tightly to the catheter. Each left vertical axis refers to the flow rate measured in ml/hr, shown as stippled columns. Each right vertical axis refers to back pressure measured in cm of water, shown as solid columns. Columns show the mean and SD of three measurements, except Clamp2 with AAF, which is based on two measurements for technical reasons.

100 ml/hr), the range of deviations was unacceptable (−40.0 to 18.5% at 10 ml/hr and −21.9 to 7.2% at 100 ml/hr). Experimental measurement errors, including an error of less than 2% for the graduated cylinder, cannot account for these large deviations. An acceptable deviation is less than 10% for each unit.

Thus, the values on the metered dials cannot be trusted. Manufacturers, apparently aware of this fact, specify the need to verify the correct flow rate by counting drops. With calibration of each DAF or SM necessary, the numerals on the metered dial are rendered at best superfluous and at worst misleading.

Besides lacking accuracy, flow rates varied significantly from one unit to another within brands. This variation could not be due to experimental errors in the drop counting technique. Sources of such error include changes in the volume per drop and time-dependent changes in drop count. The latter was ruled out by graphical analysis. The former, drop volume, is known to vary with administration set (9,10), kind of fluid (9), and flow rate (9,10). However, small drop administration sets, as used in this study, produce stable drop sizes regardless of flow rate (9). We used only fluids containing dextrose or salts, which have been shown to produce same-sized drops (9). Thus, the variations found in this study are inherent in the regulators. One cannot rely on two identically set DAFs or SMs to produce the same flow rate, even under laboratory conditions.

The second experiment demonstrated the dependence of flow rate on back pressure. For three brands, DAF, SM, and CFLO, flow rate decreased linearly with increasing back pressure. Rithalia and Rozkovec, in their in vivo study of the DAF, found the same relationship between flow rate and back pressure (8). Indeed, this correlation is predicted by basic physical principles for laminar fluid flow: ΔP equals flow times resistance. The present study demonstrates that high CFs are needed to change flow rate appreciably in vitro. For example, a CF of 4 ml/min caused a 10% reduction in DAF rate. These conditions may not hold in vivo, where venous resistance forms a series re-

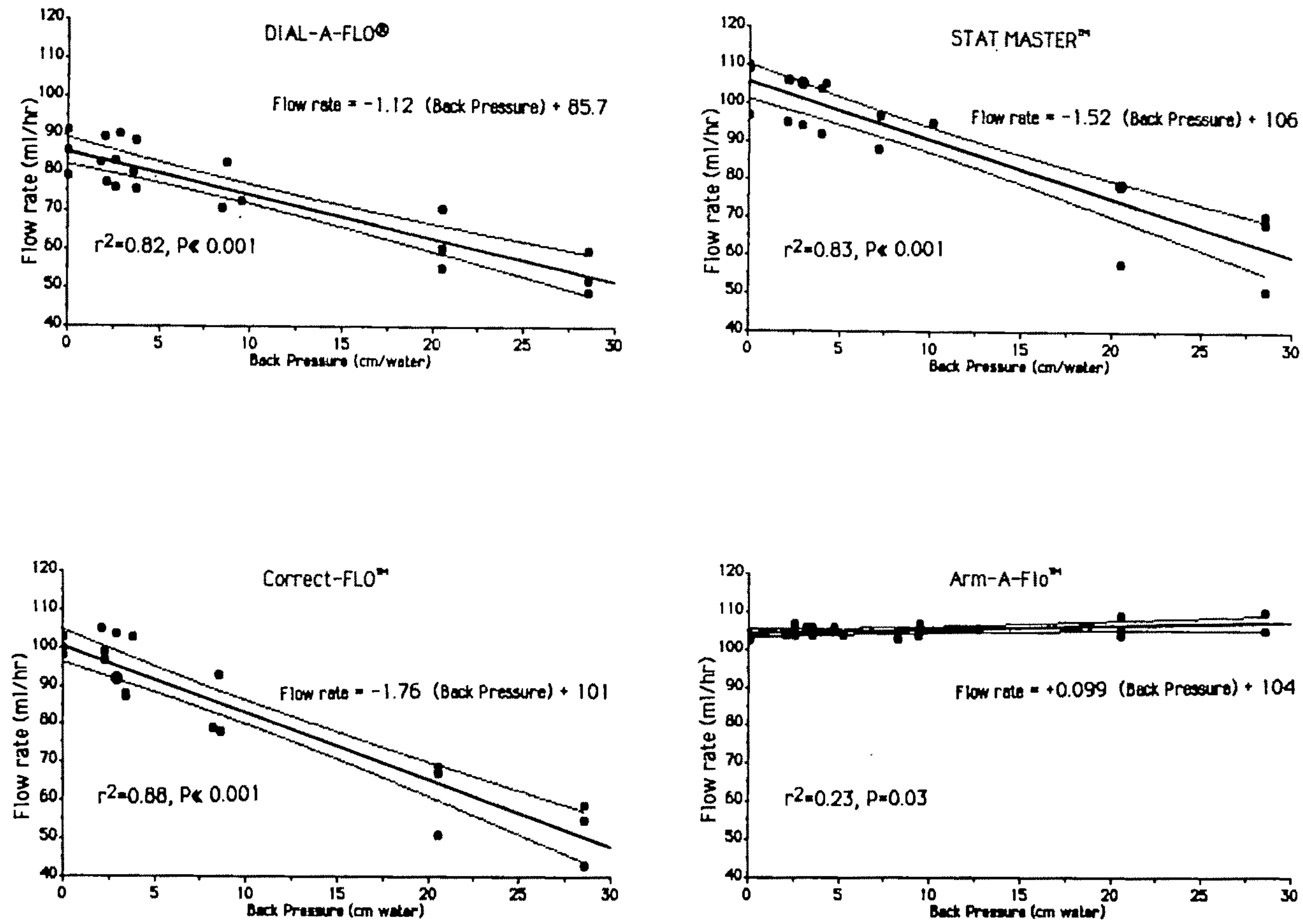

Figure 3. The data in Figure 2 shown as a scatter plot of flow rate versus back pressure. The least squares regression lines and 95% confidence intervals for the true values of flow rate are shown. Regression equations and values for r^2 for each device appear near each regression line.

sistance with the catheter, thus causing even higher back pressures for the same CF.

The AAF was the only brand tested that compensated for increases in back pressure when set to deliver 100 ml/hr. This feature of the AAF demonstrates that one cannot dismiss all resistive regulators as necessarily unreliable on the basis of simple hydraulic physics. We did not investigate the AAF at other settings owing to the difficulty encountered in setting flow rates with this device. Back pressure compensation in the AAF is achieved with a vibrating membrane that separates inlet and outlet channels (G. Rood, Armour Pharmaceutical Co., Kankakee, IL, personal communication). The membrane rapidly opens and closes the fluid path. Flow is then independent of back pressure in a manner analogous to the plateau of venous return when central venous pressure falls below the point of vena caval collapse.

It is unlikely that systematic errors in calculating flow rate from drop count data produced the results of the second experiment. Errors arising from counting accuracy were minimized by use of a hand-held toggle device. A photoelectric counter was not necessary for the counting rates found in these experiments. The major potential source of error, change in drop volume, was minimized by calibrating the minidropper over 10 min. CFs could have deviated significantly from desired rates owing to an increase in drop volume with increasing CF rate in large dropper infusion sets (9). However, such errors are not relevant to the results, since the effects of CF are mediated by back pressure, which was the variable correlated with flow rate.

There are several clinical implications of this laboratory study. First, devices with a metered dial require calibration with each use. Numerals on the dial are superfluous and may be misleading. Second, adding a CF will decrease flow rate, although high CFs are needed to decrease flow substantially. With several infusions running into a common vessel, a change

in the rate of one will reciprocally alter flow in the others. Unless one is prepared to count drops repeatedly, carrier flows and "piggyback" infusions should not be used in conjunction with a resistive flow regulator. Third, even under conditions of a single fluid path devoted to one infusion with no CF, constant bag height, and initial calibration, changes in venous pressure or resistance can, via altered back pressure, significantly affect the actual infusion rate. For example, the onset of atrial fibrillation can easily increase central venous pressure from 10 to 20 cm H_2O. Our data predict that vasoactive drug delivery regulated by a DAF would then decrease by 20%. The real danger is that this change goes unnoticed since the passive flow regulator is assumed to perform correctly despite this alteration in the patient's condition. Likewise, mechanical obstructions in the fluid path or in limb veins, a special problem in intensive care settings, occur without warning. The AAF appears to be an exception to this limitation, although tests of its compensation at several flow rates are needed.

Resistive flow regulators are useful in several circumstances. The first is when fine control of tubing resistance is desired. With the exception of the AAF, all brands of regulator tested were suited to this function. The second indication is when elimination of cold flow is desired. Although recommended as a "fail-safe" device (11), that is, one intended to place an upper limit on infusion rate (albeit an inaccurate one), a resistive regulator should only be relied upon to prevent a wide-open flow condition. Based on the results of this laboratory investigation, it is recommended that when accurate, reliable, and consistent delivery rates are needed, passive gravity-driven infusions with resistive regulators are not appropriate unless one monitors actual delivery rates by counting drops at frequent intervals. The authors believe that the problem of regulator inaccuracy is best solved by omitting flow numerals, thus forcing calibration of each unit. Also, it is reasonable to expect that continued refinements in regulator design may soon yield a device well-compensated for back pressure that is also easy to set and change.

Summary

The clinical performance of four different resistive intravenous flow regulators was simulated in the laboratory. The devices tested were the Dial-A-Flo (DAF), Stat Master (SM), CorrectFlo (CFLO), and Arm-A-Flow (AAF). Five DAFs and five SMs were tested for accuracy at each of two flow settings. Accuracy is irrelevant for the CFLO and AAF, which have no metered dial. Flow rate for the DAF deviated from the 30-ml/hr setting by $-25.1 \pm 7.2\%$ (mean ± SD) and from the 100 ml/hr setting by $-23.4 \pm 3.5\%$. The SM deviation was $-0.1 \pm 25.2\%$ at a 10 ml/hr setting and $-4.08 \pm 12.5\%$ at the 100 ml/hr setting. Actual flow varied significantly with the individual DAF or SM unit employed. For all four devices, seven conditions of varying back pressure were modeled using different carrier flow rates and catheter clamps. Data from the DAFs, SMs, and CFLOs tested at the 100 ml/hr setting showed a linear relationship between flow rate and back pressure (r^2 range, 0.82–0.88, $P << 0.001$). In contrast, AAF flow rate was relatively constant with changes in back pressure. We conclude that neither the DAF nor the SM metered dial provides accurate flow. The DAF, SM, and CFLO did not compensate for applied back pressure; the AAF did compensate for increasing back pressure, but was difficult to use. We cannot recommend any of the four brands tested for routine clinical use.

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Clinical Reports

Diazepam-Associated Posttraumatic Stress Reaction

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Stress reactions to the psychological conflicts of war have been noted since antiquity and described in detail during the latter half of the 19th century (1). Recently, a large group of Vietnam veterans has been identified as suffering from posttraumatic stress disorder (PTSD), defined in the American Psychiatric Association Diagnosis and Statistical Manual (DSM-III) as being characterized by the development of at least two of the following symptoms: startle response, sleep disturbance, survival guilt, concentration and memory impairment, and avoidance of symbolic events associated with trauma (2). Symptoms of anxiety occur in sudden attacks, triggered by associated sights or sounds (3), a feeling of loss of control (4), or even thoughts and memories alone (5). There have been sparse reports of diazepam triggering a rage reaction in patients with PTSD (6). Diazepam is an anxiolytic agent frequently used to supplement local anesthesia in endoscopic and other minor procedures as well as being a common choice for preoperative medication. This case report describes the acute stress reaction of a patient with the symptoms of PTSD to diazepam and the abrupt cessation of symptoms after the administration of IV aminophylline.

Case Report

A 39-yr-old Vietnam veteran was scheduled for elective esophagogastroduodenoscopy to evaluate hematemesis. No history of substance abuse or psychiatric history was elicited by the admitting physician. Endoscopy was performed in the operating room under topical anesthesia to the oropharynx supplemented with 15 mg diazepam given in increments of 2.5 mg. After some initial gagging, the patient cooperated with the endoscopic examination that revealed no abnormalities. The patient was transferred to the recovery room without incident. Anesthesiology consultation was requested 10 min after the patient's arrival when he began to behave in a bizarre fashion, holding his body rigidly, eyes tightly shut and hands clenched in a "karate chop" position. He was disoriented to time, person, or place and when questioned or touched, he would either respond in Vietnamese, or provide in English his name, rank, and division in the Marine Corps. He also clutched his right knee, and guarded it as though it were injured. The patient's wife was summoned but he remained disoriented and unresponsive to her as well as to the medical staff.

At this time, aminophylline 1 mg/kg IV was administered without significant effect on ECG, blood pressure, or heart rate. In addition, no symptoms of toxicity such as nausea, vomiting or convulsive activity were noted. Within 10 min, the patient rapidly became oriented to time, person, and place. He was completely amnesic for the period of unusual behavior, remembering getting ready for the gastroscopy and then waking up in the recovery room with his wife at the bedside.

Further investigation revealed that this veteran served as a translation-interrogator and squadron leader for the Marine Corps during the war in Vietnam, where he sustained injuries to his left hand and right leg, requiring surgery. He vehemently denied any form of drug use, both during the war and in the present. On close questioning, he reported that he had had two previous "flashbacks" to Vietnam, for which he is amnesic. Both episodes occurred while drinking alcohol and required physical restraint but did not result in hospitalization or treatment of post-combat

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stress disorder. Since these two acute episodes, he has avoided any alcohol intake or even pain medication for dental procedures to prevent feeling a loss of control.

Discussion

Posttraumatic stress disorder is a common psychological problem estimated to occur in 500,000–700,000 Vietnam combat veterans (7). In addition, countless World War II and Korean War veterans continue to have symptoms of traumatic war stress (8). Multiple events and experiences trigger the acute reaction. Lipkin et al. (4) assert that most clinicians experienced in treating Vietnam combat veterans have found these patients not to have a history of loss of control but rather to be overcontrolled, commonly having a fear of losing self control. Our patient articulated this fear as the reason he abstained from alcoholic beverages, psychotropic drugs and even pain medications after extensive dental repair. Certainly being in the passive role of a patient in an operating room with darkened lights for an endoscopic procedure could exacerbate feelings of helplessness.

In addition to environmental stimuli, the sedation from 15 mg of diazepam probably played at least a contributory role. Benzodiazepines have been implicated in enhancement of rage in patients suffering from PTSD (6,9). These drugs are contraindicated in the treatment of PTSD because they interfere with normal coping mechanisms (8). Yet there is a paucity of literature describing any adverse stress reactions from a single perioperative exposure to these drugs.

The reversal of psychotic symptoms by aminophylline in our patient supports the assumption that diazepam exacerbated his stress reaction. Aminophylline reversal of the CNS sedation of diazepam has been described in both a case report (10) and double-blind study (11). Both reported significant antagonism of diazepam-induced sedation with intravenous aminophylline at the dose of approximately 1 mg/kg. This dose was below that required to produce bronchodilatory or toxic effects. Although in this case the administration of IV aminophylline resulted in the prompt reversal of the central effects of diazepam, more specific antagonists will prove even more useful.

Recent investigation has demonstrated benzodiazepine receptors in the central nervous system (12), which have been shown to enhance the synaptic inhibition produced by the neurotransmitter GABA in many parts of the brain (13–15). In the past, high affinity ligands of these receptors also shared similar pharmacologic properties of the benzodiazepines, for example, triazolam or midazolam. However, current investigation of the benzodiazepine antagonist, imidazopine Ro 15-1788, demonstrates interaction with the same type and number of receptor sites as diazepam (16,17) without major pharmacological effects (13). In fact, this compound has been shown to be a potent antagonist of the major central actions of diazepam both in experimental models (18) and in clinical trials (22,23).

As military combat veterans age and require more surgical procedures, we can expect to see an increased incidence of untoward reactions to diazepam. Although aminophylline has been shown to reverse some of these effects, more specific benzodiazepine antagonists may prove even more useful in treating these patients.

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Repeated Epidural Anesthesia for Extracorporeal Shock-Wave Lithotripsy Is Unreliable

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The introduction of extracorporeal shock-wave lithotripsy (ESWL) for the noninvasive removal of renal stones has created the need for some patients to undergo multiple anesthetics over a relatively short period of time. Continuous lumbar epidural anesthesia (CLEA) has many advantages for this application but, in our experience, seems to be less reliable and behaves abnormally when repeated serially. The purpose of this study was to examine prospectively the incidence of failure and abnormal occurrences during use of CLEA for ESWL.

Methods

Institutional approval and informed consent were obtained for each subject. Seventy-one adult patients admitted for ESWL with large and/or bilateral renal stones (likely to require repeated ESWL) and no history of previous low back surgery were studied over a 3-month period. This group comprised approximately 25% of all patients undergoing lithotripsy during this period.

CLEA was performed by various members of the resident and CRNA staff on a rotating basis under the supervision of one of the anesthesiologist authors. Only occasionally did the same resident or CRNA perform repeated CLEAs upon the same patient. All had CLEA utilizing lidocaine 1.5% with epinephrine 1/200,000, which was pH adjusted with sodium bicarbonate 1 mEq/10 ml of local anesthetic, resulting in a final lidocaine concentration of 1.4%. The epidural space was identified with a standard loss-of-resistance technique with subsequent injection of local anesthetic followed by the introduction of an epidural catheter, the tip of which was placed 2–3 cm beyond the tip of the needle. The following data were collected for all subjects undergoing their initial CLEA: age, sex, height, weight, position of patient during induction of CLEA, the interspace used, the volume of local anesthetic injected, the level of sensory anesthesia after 25 min, duration of anesthesia after last dose of local anesthetic, the adequacy of anesthesia, and the need for supplementary analgesics and sedatives during ESWL. Block failures were defined by the need for another complete anesthetic, either general or spinal. Any problems encountered during the performance of the CLEA were noted. Any patient requiring repeat ESWL received CLEA in an identical fashion to the initial block, with the above data again recorded.

The frequency of failed CLEA was compared between initial and subsequent blocks using Fisher's exact test. The level and duration of sensory anesthesia were also compared in initial and repeated blocks using the paired t-test. No patient having a failed CLEA underwent subsequent CLEA during the remainder of the study period.

Results

Patients had the following characteristics (mean ± SD): age 47 ± 13 years, height (cm) 171 ± 11, and weight (kg) 76 ± 19, and 54% of the subjects were male. The incidence of failed CLEA is shown in Table 1. The proportion of failed blocks increased significantly as the number of previous CLEAs increased (Table 1). Problems frequently noted during the performance of repeat CLEAs included pain in the back and posterior thighs during injection of local anesthetic, the subjective impression of decreased compliance of the epidural space, and aspiration of bloody local anesthetic solution from the epidural needle or catheter. The pain that occurred upon injection was

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Table 1. Failure Rate of Initial and Repeat Epidural Blocks

	Epidural				
	1st	2nd	3rd	4th	5th
n	71	20	9	7	2
Failed	0	2	2	2	1
Fisher's exact test	1	2–5	1–3	4–5	
	(P = 0.0004)		(P = 0.02)		
		1–2	3–5	1–4	5
		(P = 0.003)			(NS)

directly related to the speed of injection. The incidence of these problems is shown in Table 2, categorized by the number of repeat CLEAs performed. There was no pattern with respect to the time interval between previous and failed CLEAs (range 1–69 days). The percentages of both failed and problematic CLEAs are shown graphically in Figure 1. The repeated blocks that did not fail were indistinguishable from successful initial CLEAs, despite the occurrence of the problems noted above during the performance of the block. Sensory levels at 25 min and the duration of anesthesia were similar with initial and successful repeat CLEA (Fig. 2).

None of the subjects having failed CLEA or CLEA with the noted problems had any neurologic sequelae in the postoperative period.

Discussion

The advantages of CLEA for ESWL are many. Patients often require cystoscopy prior to ESWL. CLEA allows easy maintenance of anesthesia during transportation between the cystoscopy suite and the site where the ESWL is to be performed and, in the frequent case of delay before the lithotripter becomes available, the patient may wait safely in a recovery area. This frees anesthesia personnel to care for other patients and increases the efficiency of the entire suite. General anesthesia, by comparison, requires more intensive anesthesia care during transportation and also requires that an anesthetist (and location) be tied up during the inevitable delays before the lithotripter becomes available. In addition, patients undergoing repeat ESWLs on subsequent days are better able to maintain nutrition following CLEA than they are after general anesthesia with its frequently associated postoperative nausea.

Our initial impression of decreased reliability with repeated CLEA for ESWL treatments is substantiated by the data. The incidence of failed blocks increased with the number of previous CLEAs (Fig. 1). The failure rate for all repeated blocks (seven of 38) was 18%. The increasing frequency of problems noted with serially repeated blocks in conjunction with a high failure rate raises questions: What are the causes of these problems? Should our practice of anesthesia be altered?

The pain noted on injection of local anesthetic solution into the epidural space was not radicular in quality and was dependent upon the rate of injection. This finding, in conjunction with the decreased epidural compliance during injection and the return of bloody local anesthetic solution from the needle and catheter, suggests that pathological changes may be present in the epidural space at the time of repeat CLEA. The pain and bloody local anesthetic solution are consistent with an inflammatory response while the decreased compliance and incomplete block with limited spread suggest the presence of a barrier to diffusion of the local anesthetic, including edema, hematoma, or adhesions.

Changes in the epidural space associated with CLEA for ESWL may be due to several factors: mechanical disturbance by the needle, catheter, or local anesthetic solution; associated hematoma; chemical effect of the local anesthetic solution; or the ESWL with its considerable release of shock-wave energy into the nearby retroperitoneal space.

Pathologic studies of the epidural space after CLEA are few. Delaney et al. (1) studied the effects of a single injection of lidocaine and steroid (triamcinolone acetate suspension) into the epidural space of the cat and found only minimal histologic changes after 30 days, changes that had largely resolved after 120 days. Carl et al. (2) reported granulation tissue and blood in the epidural space at autopsy after long-term morphine injection via epidural catheter. Rainbird and Pfitzner reported a case of limited spread of epidural anesthesia 3 yr after an epidural blood patch (3). Other case reports, however, document successful epidural anesthesia after epidural blood patches (4–6).

Little has been reported on the effect of multiple needle punctures, catheter insertions, or injections of local anesthetic into the epidural space. The question of hematoma formation causing resultant problems with subsequent CLEA is raised by the case report of Rainbird and Pfitzner. Hematoma formation could explain the decreased compliance of the epidural space we observed, as well as the limited spread of the local anesthetic, but would not explain the pain upon injection. Pain would be most consistent with an inflammatory process. It seems reasonable, therefore, to hypothesize that the formation of an epidural hematoma could only partially contribute to the spectrum of problems we observed.

The chemical effect of the local anesthetic injected

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Table 2. Abnormal Occurrences Noted during Performance of Epidural Blocks

Epidural number	*n*	Days since previous epidural block	Abnormal occurrences
1st	71	—	One—low compliance
2nd	20	1,1	Two—failures
3rd	9	15	One—failure
		5	One—failure + pain
		2	One—pain
		71	One—low compliance + bloody local anesthetic
4th	7	3	One—pain + low compliance + bloody local anesthetic
		69	One—failure + low compliance + bloody local anesthetic
		3	One—failure + low compliance + bloody local anesthetic + pain
5th	2	8	One—failure + bloody local anesthetic
		21	One—pain

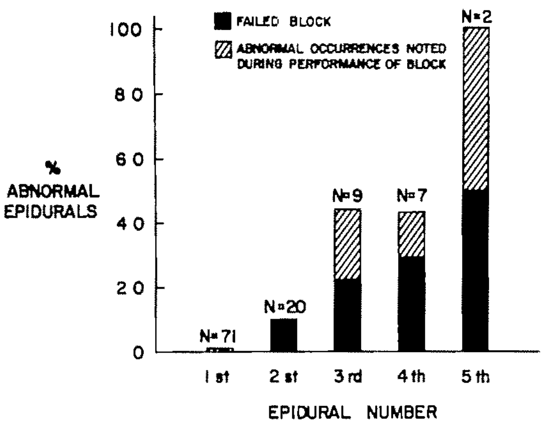

Figure 1. The percentage of epidural anesthetics that failed or were associated with unusual occurrences during the induction of anesthesia (pain upon injection, decreased epidural compliance, and return of unusually bloody local anesthetic via the epidural needle or catheter) is categorized by the number of repeated blocks.

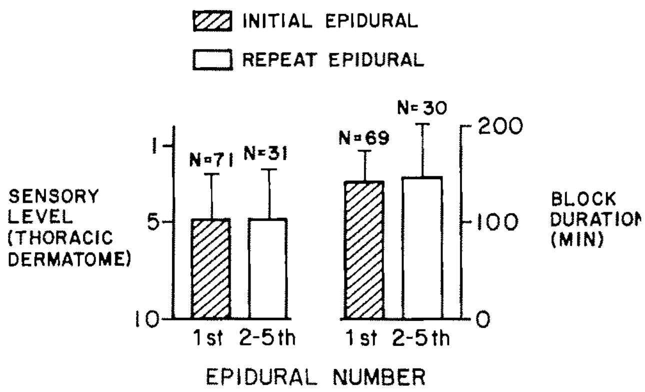

Figure 2. The level of sensory blockade after 25 min and the duration of the final dose of local anesthetic until complete recovery with initial and with repeat epidural anesthetics (mean ± SD).

Table 3. Characteristics of pH-Adjusted and Unadjusted Lidocaine Solutions[a]

	pH adjusted	Unadjusted
Lidocaine concentration (%)	1.4	1.5
pH	7.2	4.5
Osmolarity (mosm)	474	331
Sodium metabisulfite (mg/ml)	0.5	0.5
Citric acid (mg/ml)	0.2	0.2

[a]pH-adjusted lidocaine was prepared by adding 1 mEq sodium bicarbonate to each 10 ml of stock lidocaine solution (1.5% with epinephrine 1/200,000; ASTRA Pharmaceutical Products, Inc., West Borough, MA).

in our study may be implicated as a contributing factor in explaining our findings. The pH adjustment of lidocaine with epinephrine by the addition of sodium bicarbonate decreases the onset time and improves the reliability of epidural anesthesia (7). The pH-adjusted solution, however, is more hypertonic than other solutions commonly used (Table 3). Likewise, the preservatives, sodium metabisulfite and citric acid, when injected repeatedly in large volumes may contribute to an inflammatory response. The pathologic effect of these solutions would best be assessed by using an animal model, a project we are currently undertaking.

The last, and perhaps most likely, explanation for the problems we observed is the effect of the lithotripter shock waves upon the epidural space. Substantial energy is generated by the lithotripter beam. The size of the wave path and the distribution of its energy are not well described. Judging from the distribution of tenderness and bruises commonly observed on patients' backs after ESWL, it seems likely that some of the shock wave travels through the epidural space. The release of this energy into surrounding tissues is greatly increased by the presence of an air/fluid interface (8). The loss-of-resistance technique used to locate the epidural space in our study involved

the use of a small volume of air in the glass syringe that was injected into the epidural space in some patients. The resulting air bubbles in the epidural space could, possibly, cause epidural tissue damage from the shock wave. This interaction between CLEA and ESWL would explain why problems such as we observed had not been described with CLEA prior to the introduction of lithotripsy.

In summary, we describe a previously unreported problem of poor reliability with repeated epidural anesthetics for ESWL. Possible causes of this phenomenon are discussed. We recommend that the injection of air bubbles into the epidural space be avoided to minimize possible harmful effects of the lithotripter's shock wave upon epidural tissue. Further study using an animal model to assess the pathologic consequences of serially repeated epidural anesthetics and ESWL is needed.

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Venoarterial Cerebral Perfusion for Treatment of Massive Arterial Air Embolism

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Massive air embolism during cardiopulmonary bypass (CPB) is a rare but highly lethal complication. Permanent neurologic injury or prolonged recovery are common in survivors. In almost all cases the causes of massive arterial air embolism during CPB are preventable. Treatment of arterial air embolism includes elimination of the air leak, steep Trendelenburg position, and venting of the aortic root. Temporary retrograde perfusion of the cerebral circulatory system through the superior vena cava may also be performed. We present a case of massive arterial air embolism caused by a cardiac bypass pump failure coupled with "human error" by the perfusionist. The patient was successfully treated with venoarterial perfusion through the superior vena cava.

Case Report

The patient was a 6-yr-old boy with transposition of the great vessels, single ventricle, and subaortic stenosis. At age 2 months pulmonary artery banding was performed because of excessive pulmonary blood flow and progressive congestive heart failure. After cardiac catheterization at age 11 months he sustained ischemic injury to the brain in the distribution of the right middle cerebral artery manifest by left-side seizures and weakness. Over the subsequent 3 months the seizure activity ceased and left-side strength increased. At 6 yr of age he was scheduled for resection of the subaortic stenosis.

Anesthesia was induced with sufentanil 1 μg/kg body weight, thiopental 2 mg/kg, and ketamine 1 mg/kg. After the administration of pancuronium 0.2 mg/kg, the trachea was intubated. Anesthesia was maintained with a sufentanil infusion 0.3 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ and 0.4% isoflurane in oxygen. Resection of the subaortic stenosis was performed transventricularly without difficulty. After conclusion of cardiopulmonary bypass, the cardioplegia perfusion line was used to continuously aspirate blood from the aortic root (reverse flow) as an air venting maneuver. At that time a brief power outage to the bypass machine occurred. Power was rapidly reestablished but the cardioplegia venting line was inadvertently activated in the forward direction. A large column of air was consequently pumped into the ascending aorta during normal cardiac function. Core body temperature at that time was 36°C. The patient was placed in steep Trendelenburg position. Air was rapidly evacuated from the metabolic and aortic perfusion lines (still in place) and pump flow was reestablished. Methylprednisolone 20 mg/kg and thiopental 20 mg/kg were administered. The patient was cooled to 30°C and the ascending aorta was cross-clamped. Venoarterial perfusion was then performed. The superior vena cava was perfused retrogradely with oxygenated blood at a pressure of 40 mm Hg while the aortic cannula was divided and opened to the atmosphere as a vent. During the venoarterial perfusion, the coronary arteries were perfused with the blood cardioplegia cannula below the aortic cross-clamp. After 60 sec of retrograde perfusion, a large shower of small bubbles exited through the aortic cannula. Perfusion was continued for 8 min. After venoarterial perfusion, cardiopulmonary bypass was reinstituted in the normal fashion. The patient was warmed to 36°C and cardiopulmonary bypass was terminated with difficulty. The patient was taken to the intensive care unit where mechanical ventilation was continued. Four hr postoperatively the patient began moving all extremities but more on the right side than on the left. Twelve hr after surgery he developed focal motor seizures involving the left arm and leg. Phenobarbital administration was begun and the seizures were controlled. Twenty-four hr after surgery he became more arous-

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able and his mental alertness increased. Ventilatory support was gradually withdrawn and the trachea was extubated 36 hr after surgery. He continued to improve and was transferred out of the intensive care unit on the fourth postoperative day. Postoperative neurologic evaluation demonstrated left temporal hemianopsia and mild left-side weakness.

Physical examination revealed a left visual field defect and weakness of the left arm and leg. A cerebral CT scan revealed an area of infarction and cerebral edema in the distribution of the right middle and right posterior cerebral arteries. During the next 9 days left arm and leg strength returned to normal and the left visual field defect decreased. The patient was discharged on the tenth postoperative day. Phenobarbital was continued at the time of discharge.

Discussion

Massive arterial air embolism is fortunately an uncommon complication of cardiopulmonary bypass. The incidence is 0.1–0.2% (1). When it does occur, however, death or permanent neurologic impairment often result. The most common cause of massive arterial air embolism during cardiopulmonary bypass is a reduction in the oxygenator blood level. Despite the use of safety devices, unusual circumstances still develop and arterial embolism occurs (2). An event such as ours would not have been detected by sensing devices at the pump heads or oxygenator because the air infusion occurred in a line used for aspiration.

If arterial embolism occurs, the patient should be placed in steep Trendelenburg position, and blood should be aspirated from the aortic root. Other recommended measures include induction of hypothermia and administration of corticosteroids and barbiturates. The technique of venoarterial perfusion has had extremely limited use in humans (3). Animal studies indicate that 50% of embolized air can be removed from the cerebral circulation with venoarterial perfusion. It is recommended that venoarterial perfusion be performed at a pressure of 40 mm Hg for 5–10 min or until no more bubbles appear in the aortic vent (4). Hyperbaric oxygen therapy may be beneficial but is not readily available at most hospitals (5). Barbiturate therapy may be effective for conditions producing diffuse focal cerebral ischemia (6). In our case, as in most clinical situations, the amount of air introduced into the cerebral circulation is unknown. We did, however, recover a substantial number of small bubbles from the aorta.

In summary, we present a case of massive arterial air embolism in a 6-yr-old child immediately following termination of CPB. Removal of embolized air from the arch vessels confirmed the diagnosis. Therapy consisted of venoarterial caval perfusion, corticosteroids, and barbiturates. The child sustained a mild cerebrovascular insult from which he rapidly recovered with minimum residual deficits. Further research is necessary to establish the efficacy of venoarterial perfusion in removing embolized air from the cerebral circulation.

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The Temporomandibular Joint and Tracheal Intubation

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The temporomandibular joint is frequently taken for granted in patients about to undergo tracheal intubation. It is uncommon in an otherwise healthy patient not to be able to open the mouth and jaw for intubation, but in some patients this can be a problem, as illustrated by the following case report.

Case Report

A 26-yr-old Asian woman, height 154 cm, weight 54 kg, gravida 1 para 0, was admitted at 18 weeks gestation with a rapidly enlarging lower abdominal mass. She was scheduled for exploratory laparatomy under general anesthesia. A preanesthetic visit was made, and the patient was found to be otherwise healthy. History, physical examination, and laboratory evaluation were normal and noncontributory. The next day general anesthesia was induced with thiopental and, after establishing an adequate airway, succinylcholine was administered. Multiple attempts at intubation were unsuccessful as the teeth could not be separated more than 4 mm. Several attempts at blind nasotracheal intubation were also unsuccessful. After approximately 45 min, the surgical and anesthetic procedures were abandoned.

Two days later, faced with the increasing size of the lower abdominal mass, thought to be an ovarian tumor, the patient was again scheduled for surgery. Preanesthetic evaluation showed the patient could readily open her mouth, but a forward thrust of the mandible was noted. Applying backward pressure on the mandible prevented her from opening her mouth.

With the observation that the mandible could indeed be opened widely with forward movement of the mandible, anesthesia was induced with thiopental, and with an adequate airway, succinylcholine was administered. Intubation was readily accomplished by opening the mandible with a forward pull, allowing ready exposure of the larynx and intubation. The procedure was continued without difficulty and a large malignant ovarian cystadenoma was found, which caused the patient's death approximately 2 months later. Radiographs of the mandibular joints taken postoperatively showed only a prominence of the articular tubercle.

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Discussion

The temporomandibular joints are the only joints in the body that have essentially two movements (Figs. 1, 2). Each joint consists of a hinge joint with a movable socket (ginglymus). Opening of the mandible requires a rotation within the hinge portion of the joint (Fig. 1, *IB*) and a sliding forward of the mandibular condyle over the articular tubercle (Fig. 2, *IIA*). As one opens the mandible, there is initially a rotational movement within the capsule of the joint, and then a combined further rotation and sliding of the mandibular condyle forward (1,2). These movements can be readily appreciated if one places a finger just anterior to the tragus of the ear and feels for the movement of the condyle in the rotation and sliding (or translatory plane) of the joint. The normal rest position of the mandible is with the jaw slightly open, 3–4 mm, using only the slight rotational movement of the mandibular condyles. With unconsciousness or complete relaxation of the muscles of the mandible and mastication, the jaw may slide forward and thus open more widely. The joints are generally freely moveable, in that during mastication one mandibular joint may be thrust anteriorly while the other one may be held posteriorly to allow rotational movement in occlusion of the teeth, or both may be thrust forward to allow the biting or shearing mechanism of the incisor teeth (Fig. 2, *IIB*). The capsule of the joint is divided into two compartments by an interposed fibrocartilaginous disc, which serves in part as the articulating surfaces of the bony components.

The case presented illustrates the unusual problem of not being able to open the mandible once the patient has been anesthetized and thoroughly relaxed in

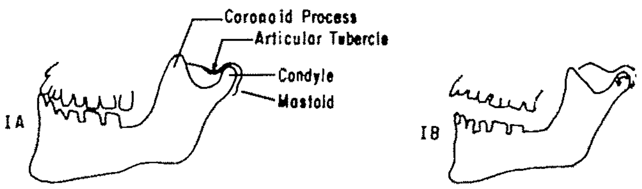

Figure 1. (IA) Bony components of the temporomandibular joint. (IB) The initial rotation of the condyle of the mandible.

preparation for intubation. In this particular patient, either a slight irregularity or prominence on the articular surface of the temporomandibular joint obstructed the forward sliding motion of the mandible so that the jaw could not be opened, or the articular disc was deformed, which obstructed free movement. The maneuver of pushing or pulling the mandible forward was not performed during the initial attempts at intubation. Should this problem arise again in the future, one should remember that a sliding component may be very essential, and one may either push forward from the angles of the mandible to help slide or move the mandible forward, or the anterior of the mandible may be grasped and pulled forward.

This case represents a somewhat unusual problem, as many patients with arthritic changes in the temporomandibular joint find they can open the mandible easier by avoiding the translatory or sliding movement. Painful conditions especially may be more comfortable if the translatory movement is avoided (2). The fibrous disc may become deformed, and serve to trap or block the translatory movement, a possible cause of this patient's problem. Dislocation of the mandible, on the other hand, results when the mandibular condyle is forced too far forward of the articular tubercle and is then held there by the forces of the masseter muscles.

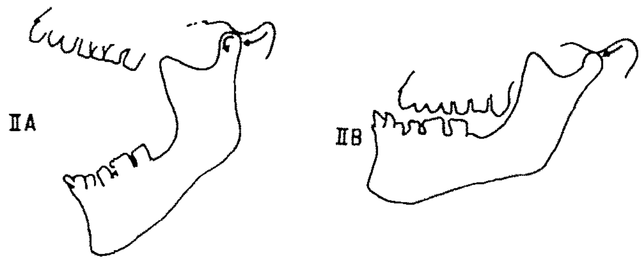

Figure 2. (IIA) After initial condylar rotation, the condyle slides forward over the articular tubercle. (IIB) Sliding forward of the condyle for incisor biting with closure of mandible.

Other causes of the inability to open the mandible may occur, such as a fracture of the zygoma, which may trap the coronoid process of the mandible behind the arch of the zygoma. Trauma in this area may produce swelling and hematoma that may also limit this movement of the mandible.

In summary, though the temporomandibular joints are usually considered of little consequence during tracheal intubation, it should be realized that there may be limitations in movement, and that the forward sliding motion of the joint may be very important to obtain an opening of the mandible wide enough to permit laryngoscopy and tracheal intubation.

Thanks to Mrs. Josie Kirsch for secretarial assistance, and to Drs. Mark Bowden and John Angelillo for reviewing the case and the manuscript.

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Grand Mal Seizures after 2-Chloroprocaine Epidural Anesthesia in a Patient with Plasma Cholinesterase Deficiency

Arthur R. Smith, MD, Dongzin Hur, MD, and Fernando Resano, MD

2-Chloroprocaine is an ester-linked local anesthetic with low potential for systemic toxicity because of its rapid hydrolysis by plasma cholinesterase to 2-chloroaminobenzoic acid and 2-diethylaminoethanol, two inactive metabolites (1). We observed a patient who developed grand mal seizures after the epidural injection of 2-chloroprocaine for cesarean delivery. Subsequent plasma analysis demonstrated absence of plasma cholinesterase and a dibucaine number of 0.

Case Report

A 20-yr-old woman was admitted in labor at 37 weeks gestation of an intrauterine pregnancy with breech presentation. The patient had no significant medical history, except for seasonal asthma during adolescence. She had had no previous anesthetic administration. The family history of anesthesia was unremarkable. The physical examination and review systems were unremarkable. She weighed 62 kg and was 148 cm in height.

Although pregnancy and labor had been uneventful, the decision was made to perform a cesarean section under epidural anesthesia. Using the loss of resistance technique, the epidural space was entered at the L3-4 interspace with a 17-gauge Tuohy needle after several attempts. After aspiration negative for CSF or blood, and a test dose of 4 ml of 3% 2-chloroprocaine, 15 ml of 3% 2-chloroprocaine was injected through the needle in four divided doses over 6 min. An epidural catheter was then advanced and, after another aspiration negative for CSF or blood, 1 ml of 3% 2-chloroprocaine was injected to establish catheter patency. Total dose administered was 600 mg.

Satisfactory anesthesia was established to the sixth thoracic dermatome and surgery was begun 15 min after the last injection of local anesthetic. The patient was comfortable although she complained of drowsiness and dizziness. Four minutes after incision, a healthy baby girl was delivered with Apgar scores of 9 at 1 and 5 min. Shortly after the delivery of the infant, the patient had onset of tonic–clonic seizures, limited to the arms and face, with loss of consciousness and hypotension (blood pressure 80/40 mm Hg).

The patient was oxygenated and succinylcholine, 100 mg IV, was given to facilitate tracheal intubation. Blood pressure was restored to normal levels with 10 mg ephedrine IV. She received no other medication except for pitocin IV.

At the end of surgery, the patient was apneic, unresponsive to verbal commands, and showed no discernible response to a peripheral nerve stimulator. She was mechanically ventilated for 3.5 hr until she was awake and able to be extubated (i.e., could sustain a head lift for 15 sec). At this time, there was no residual sensory blockade from the epidural anesthetic.

Immediately after the operation the plasma cholinesterase level was 0 U/ml and the dibucaine number was 0 as determined by the Dupont ACA method (2). These findings were confirmed several months later. She made an uneventful recovery without sequelae.

Discussion

The rapid hydrolysis of 2-chloroprocaine by plasma cholinesterase limits its potential for systemic toxicity in patients with normal enzyme levels. Kuhnert et al. (3) measured plasma levels of this local anesthetic in obstetrical patients and concluded that the lowered plasma levels of plasma cholinesterase present at term (4) are adequate to hydrolyze most of the anesthetic diffusing into the blood and no chloroprocaine was detected 25–30 min after epidural anesthesia. Recently, the same author reported the mean apparent maternal 2-chloroprocaine half life after epidural anesthesia to be 3.1 minutes with ranges from 1.5 to 6.4 min (5).

The lack of sequelae after an apparent intravascular

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injection of 2-chloroprocaine (6) to a pregnant patient indicates the wide margin of safety for this drug when the plasma cholinesterase levels are normal. However, a patient with a genetic variant for plasma cholinesterase may develop abnormal reactions to 2-chloroprocaine. Kuhnert et al. (7) reported a postpartum patient with abnormal plasma cholinesterase who developed excessive somnolonce and a prolonged epidural block after 2-chloroprocaine injection.

She was either homozygous for the atypical plasma cholinesterase variant or heterozygous with one gene for the atypical variant and one gene for the silent variant. Our patient had drowsiness prior to the development of seizures. The administration of succinylcholine and subsequent prolonged apnea lead to the suspicion of the presence of a genetic variant for plasma cholinesterase.

The catheter was not tested for intravascular placement in the present case, but only one ml of anesthetic solution was injected through the catheter, which is unlikely to produce a systemic reaction. The onset of seizure activity approximately twenty minutes after the injection of the local anesthetic precludes toxicity from intravenous injection. Rather, we hypothesize that the systemic absorption of the local anesthetic from the epidural space without hydrolysis produced a toxic blood level (8). Clinically this was manifested by drowsiness and then a seizure restricted to the areas which did not have a motor blockade.

In summary, we describe a case of grand mal seizures following epidural anesthesia with 2-chloroprocaine in a patient with complete absence of plasma cholinesterase. To our knowledge, it has not been reported previously in the literature. The appearance of unusual drowsiness after a regional block with 2-chloroprocaine should warn the anesthesiologist of possible abnormal high plasma levels of the local anesthetic due to low plasma cholinesterase level because of genetic variant.

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Epidural Bubbles as a Cause of Incomplete Analgesia during Epidural Anesthesia

Bernard Dalens, MD, Jean-Etienne Bazin, MD, and Jean-Pierre Haberer, MD

Several complications can occur during epidural anesthesias (1,3,4); most of them can clearly be related to the drug administered, the patient's clinical status, and/or the technique used. One of the most irritating incidents is the abnormal distribution of sensory blockade with painful gaps in areas that would normally be completely anesthetized.

We report two cases of epidural administration of local anesthetics in young children with subsequent incomplete analgesia, which we relate to the technique used for detecting the penetration of the needle into the epidural space.

Case 1

A 5-yr-old boy, 103 cm in height and weighing 18.5 kg, was admitted because of intermittent difficulties in walking and hemithoracic pain. Physical examination was unremarkable, as were laboratory findings. Spine roentgenograms showed a large paravertebral mass adjacent to the right side of T-7, T-8, and T-9, with collapse of the T-7 vertebral body.

After informed consent from the parents, the child was scheduled for thoracotomy for tissue diagnosis under both general anesthesia with assisted ventilation and lumbar epidural analgesia (for postoperative pain relief). To confirm the hypothesis of medullar compression, we decided to add isotonic contrast agent (Iopamiron 200) to the local anesthetic mixture (0.5% bupivacaine with 1:200,000 epinephrine).

The epidural space was approached with the child anesthetized and placed in the lateral decubitus position, as is usual in our department (2), and penetration of the needle into this space was detected with an air-filled syringe.

Radiographic examinations (Figs. 1 and 2) produced evidence of compressive disorders at T-9 level where the radiopaque solution was stopped. Also, the films

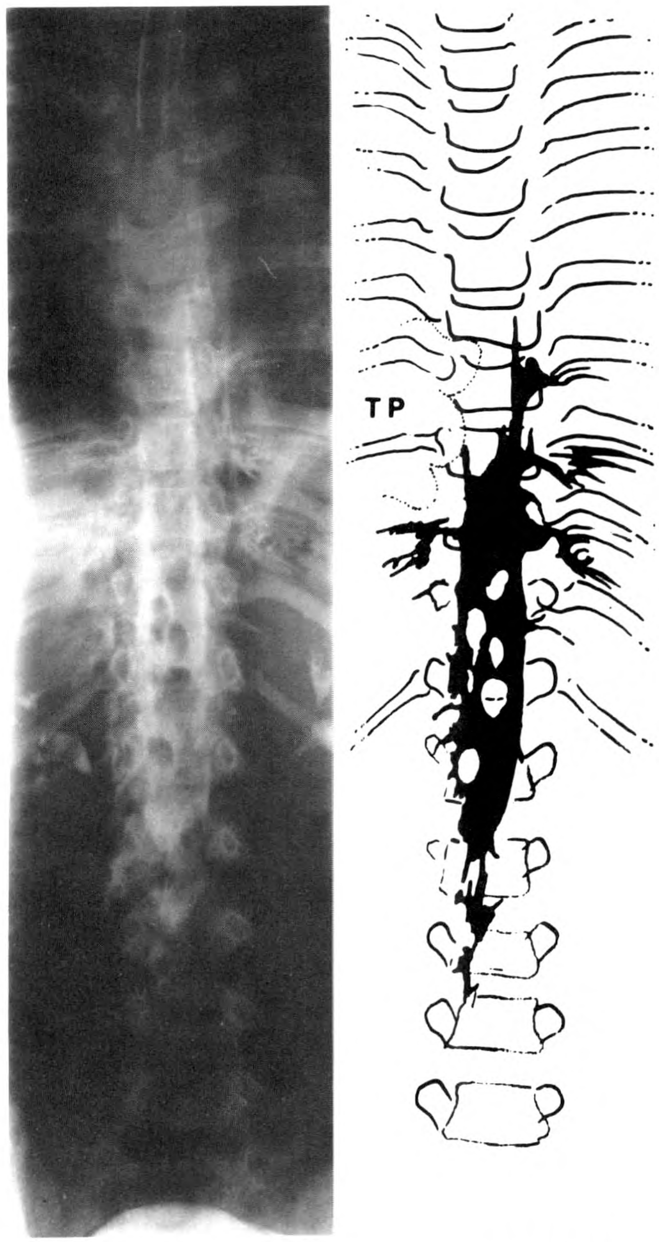

Figure 1. Front view peridurogram in case 1. The left part is the x-ray, the right part represents the findings of the x-ray in diagrammatic form. Note the right opacities facing T11–12 and L-2 vertebral bodies. The opacification of the urinary tract was the result of preoperative intravenous urography. The region marked TP is the limits of the tumor process (dotted line), impairing the cephalad progression of contrast material in the epidural space.

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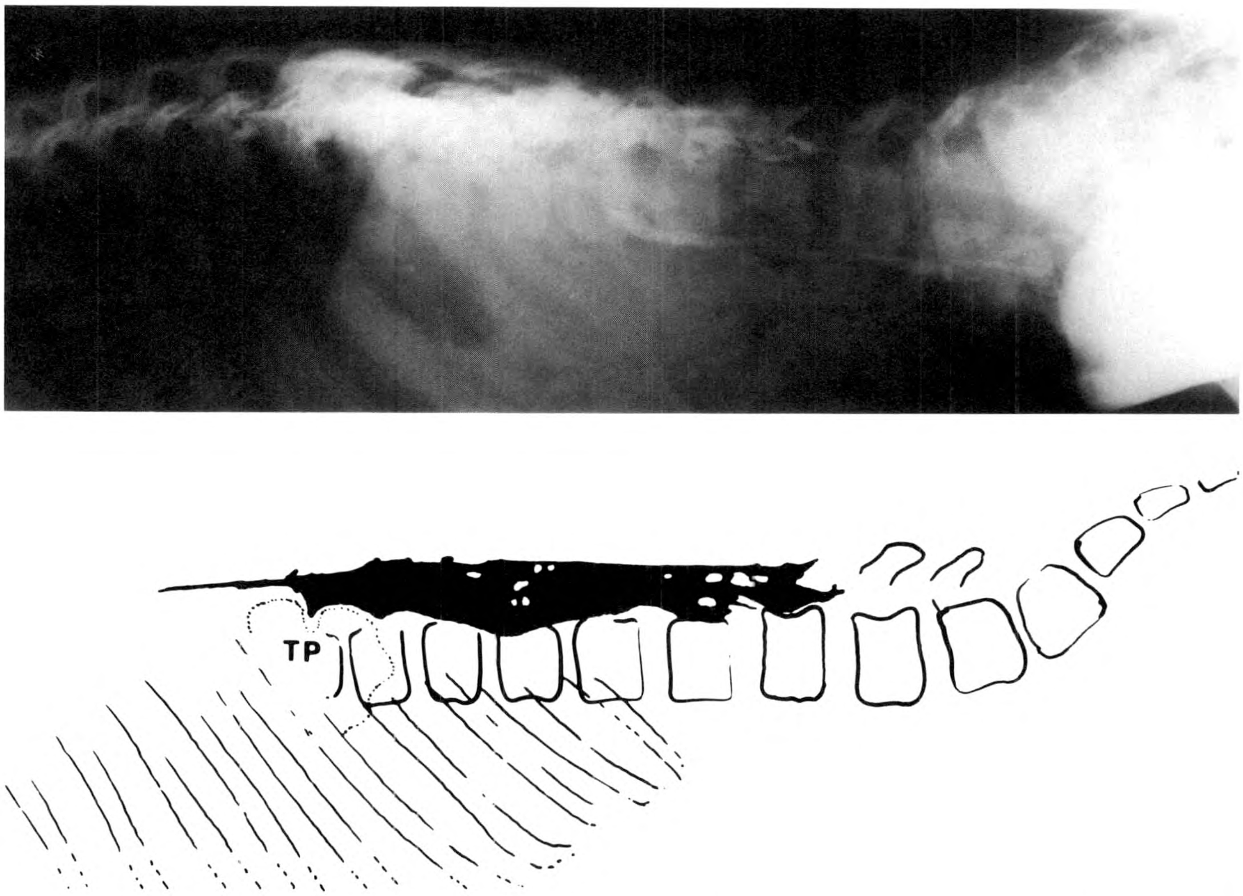

Figure 2. Lateral view peridurogram in case 1. The top is the x-ray, the bottom represents the findings of the x-ray in diagrammatic form. Note the medial opacities facing T11–12 and L-2 vertebral bodies. The opacification of the urinary tract was the result of preoperative intravenous urography. The region marked TP is the limits of the tumor process (dotted line), impairing the cephalad progression of contrast material in the epidural space.

showed several clear opacities, regularly rounded and looking like air-filled bubbles, which probably were a consequence of the air-detection technique. Some of these bubbles (Fig. 1) were medial in the front view (T-11, T-12, and L-1 vertebral bodies) and others were lateral (right part of the vertebral canal, at the level of T11–12 and L-2 vertebral bodies). In the lateral view (Fig. 2), the bubbles were more difficult to identify, but some were posterior and others lateral, especially at the T-12 and L-2 levels.

Once the child woke up, at the end of the surgical procedure, we evaluated the level of the sensory blockade and found three painful areas within the "anesthetized" territory: 1) a large one in the lower part of the abdominal wall, just above the right inguinal region (T-12 area); 2) a small one below the right inguinal region (L-2 area); and 3) a large one (separated from the previous one) in the medial part of the right thigh (L-2 area).

Case 2

This 4-yr-old boy, 101 cm in height and weighing 19.5 kg, was admitted for a tumor in the lumbar area similar to that in case 1. Physical and laboratory examinations were normal and, as in the previous case, the child was scheduled for operation for tissue diagnosis under lumbar epidural anesthesia with light general anesthesia (0.25% halothane in 65/35 N_2O/O_2). A peridurography was performed (Figs. 3 and 4) after the child was anesthetized. Roentgenograms did not reveal any compression but showed several air-filled bubbles within the vertebral canal.

When it was assumed that sensory blockade was complete, the surgical procedure began. The skin was cleaned. Drapes were placed and fixed to the skin with forceps: when the third forceps was put on the lower part of the abdominal wall just above the right inguinal area (T-12 area), the child immediately woke

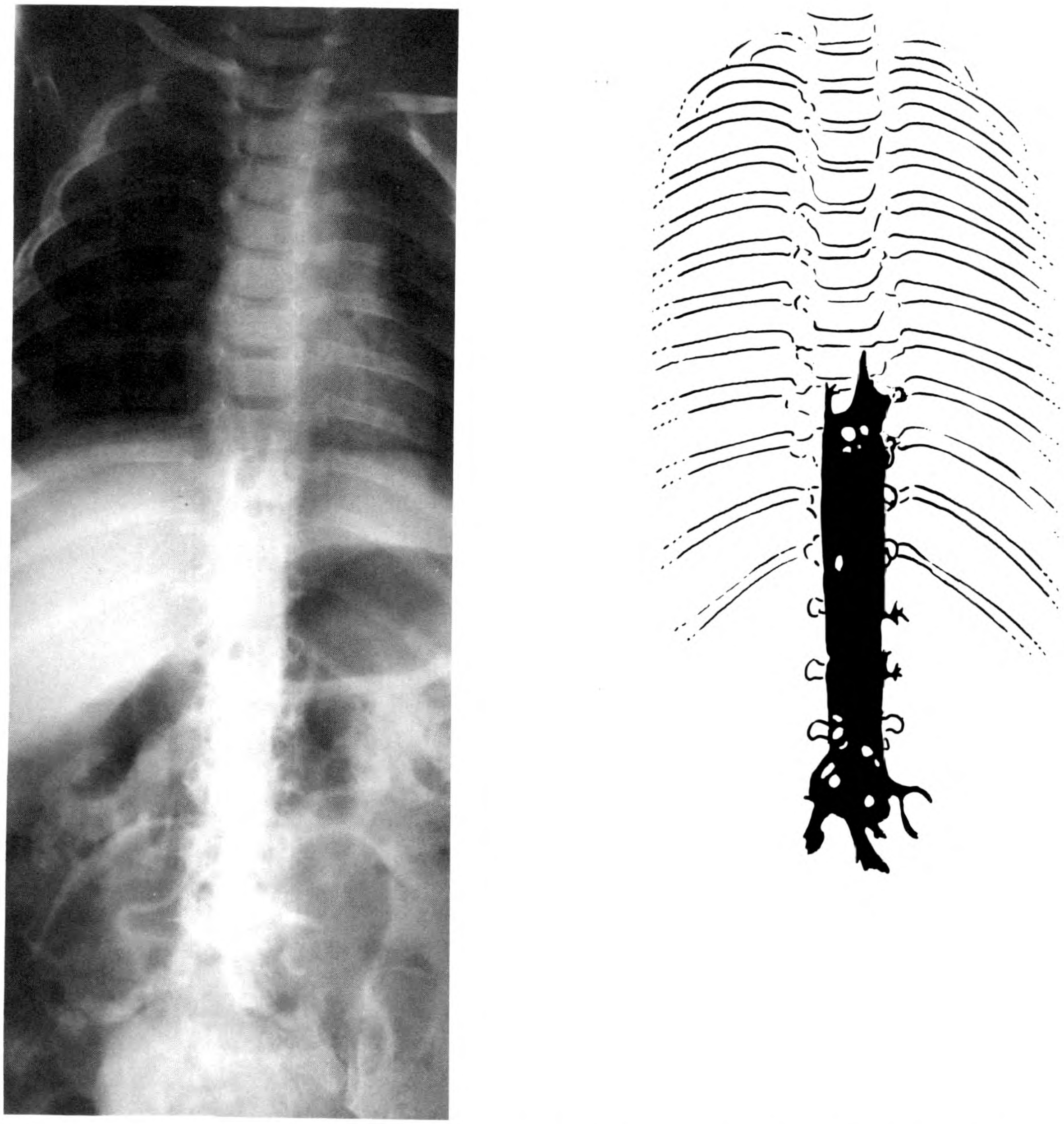

Figure 3. Front view peridurogram in case 2. The left part is the x-ray, the right part represents the findings of the x-ray in diagrammatic form. The epidural bubbles are small-sized (probably due to the high concentration of contrast material in the epidural space) and widely spread. Note the right-sided bubbles at T-12 and L3–4 levels. Note also the left-sided bubbles (L3–4 levels) that were not associated with unanesthetized dermatomes.

up and cried (general anesthesia was very light). The forceps was slightly displaced and the child quietened. Any new attempt to put the forceps in the previous zone instantly produced evidence of pain.

At the end of the procedure, we evaluated the upper limit of sensory blockade, which was T-8 (right side) and T-7 (left side), approximately one segment above the upper limit of the radiopaque solution (Fig. 3). Two segments were found that were not anesthetized: the first one in the area where the third forceps was initially placed (right T-12 area), and the second one in the external part of the right thigh (L-3 or L-4 area).

When reevaluating the films, we were impressed by the presence of right lateral bubbles in the front views (Fig. 3), one facing T-12 and the other superimposed on the L3–4 vertebral bodies (corresponding to spinal segments that were not anesthetized). Also,

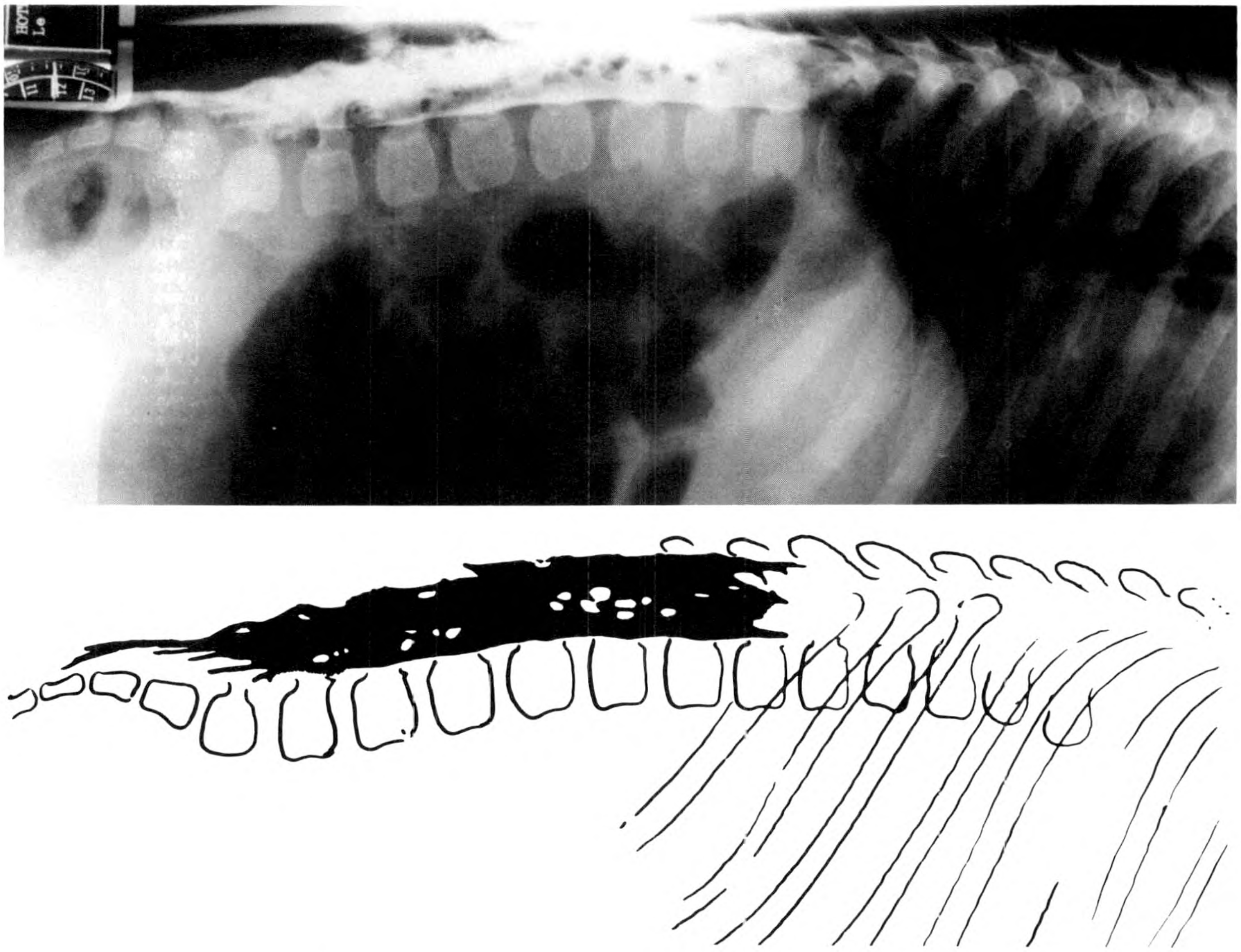

Figure 4. Lateral view peridurogram in case 2. The top is the x-ray, the bottom represents the findings of the x-ray in diagrammatic form. Note the medial bubbles at T-12 and L2–4 levels.

the lateral view (Fig. 4) revealed bubbles located very posteriorly and bubbles medial to the vertebral canal, particularly numerous at the T-12–L-1 and, to a lesser extent, L-3 levels. The films also revealed three small and left-sided bubbles facing L3–4 vertebral bodies, but the left L3–4 dermatomes were anesthetized.

Discussion

These two patients were admitted for similar conditions and were scheduled for operations for tissue diagnosis under lumbar epidural anesthesia. The clinical circumstances prompted us to use contrast material to display abnormalities within the vertebral canal, and this allowed us to find air-filled bubbles within the epidural space. These bubbles probably resulted from the loss of resistance technique used to ensure the correct positioning of the Tuohy needle. This technique consisted of connecting an air-filled syringe with the Tuohy needle, then introducing the needle into the skin towards the ligamentum flavum while positive pressure was exerted on the air trapped in the syringe. The loss of resistance perceived when the bevel of the needle entered the epidural space was associated with the injection of a small quantity of air into this space, and this was, in our minds, the origin of the bubbles shown on peridurograms.

Both patients experienced the same complication of epidural anesthesia, i.e., irregularly disseminated areas of incomplete analgesia. When reevaluating A-P films, we were impressed by the presence of lateral bubbles located at spinal levels corresponding to unanesthetized dermatomes. The hypothesis that these bubbles were causally related to the presence of painful gaps in areas that would normally be completely anesthetized was supported by the presence of medial bubbles superimposed on corresponding spinal segments in lateral view peridurograms, thus suggesting

that they were located near the emergence of spinal nerves. If bubbles in such a location are large or numerous enough, they can probably decrease the accessibility of nerves to local anesthetics with subsequent incomplete analgesia in relevant areas, as in our patients.

However, most of the bubbles remained close to the dura mater in a medial position, with no effects on sensory blockade, which is probably why epidural anesthesia is usually reliable whatever the techniques used to ascertain correct positioning of needles are.

The reasons why some bubbles could migrate laterally remain unclear. Lateral positioning of patients during the epidural approach and the often considerable extension (5) of the epidural space along spinal nerves and rami in children probably played a significant role.

The present cases demonstrate, however, that the technique of ascertaining the correct positioning of the needle into the epidural space by the loss of resistance to an air-filled syringe may have disadvantages. Loss of resistance has gained general acceptance (6), especially in small children (7) because of the risk of diluting the anesthetic mixture when a liquid-filled syringe is used. However, this risk seems minor when compared with the risk of incomplete analgesia.

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High-Frequency Jet Ventilation for Resection of Congenital Lobar Emphysema

Hiroshi Goto, MD, Steve T. Boozalis, MD, Kirk T. Benson, MD, and Kasumi Arakawa, MD, PhD

Congenital lobar emphysema (CLE) results from obstruction of a lobar bronchus usually involving a single lobe. Although the etiology of this condition is unknown in over 50% of the cases, the most common cause appears to be bronchial collapse due to abnormality or absence of cartilage (1). The condition is usually diagnosed between birth and 6 months of age, with the majority of cases found in the first month of life. As air continues to hyperinflate the involved lobe, cardiopulmonary compromise occurs. The patient usually presents with cyanosis, dyspnea, wheezing, tachypnea, coughing, and decreased breath sounds on the involved side. Occasionally a superimposed pulmonary infection exacerbates the condition, prompting hospital admission and medical treatment of the pneumonia followed by surgical treatment of the CLE. We now report a case in which high-frequency jet ventilation (HFJV) was successfully used during the resection of right middle CLE in a 3-month-old infant.

Case Report

A 3-month-old, 4.4-kg female infant presented to the pediatric clinic with cyanosis, tachypnea, decreased breath sounds on the right, and a temperature of 37.6°C. Chest x-ray showed hyperinflation of the right middle lobe and atelectasis of the right upper and lower lobes (Fig. 1). A diagnosis of right middle lobe CLE with probable pneumonia in the remainder of the right lung was made and the patient was admitted to the hospital. Over the subsequent week, vigorous pulmonary toilet and antibiotic therapy were administered. The child's respiratory rate slowed to normal ranges, the cyanosis resolved, and she became afebrile. The decision to remove the right middle lobe surgically was then made.

The patient was taken to the operating room and had the following monitors applied: blood pressure cuff, ECG, precordial stethoscope, and pulse oximeter. The initial vital signs were blood pressure 104/40 mm Hg, heart rate 150 beats/min, respiratory rate 35/min with an O_2 saturation of 98%. Preoxygenation was followed by a halothane in oxygen insufflation through a modified Mapleson D (Bain) circuit, which allowed the patient to breathe spontaneously (no positive pressure ventilation—PPV). With the patient at a good anesthetic depth with 2.5% halothane, 20-gauge intravenous and 22-gauge right radial arterial lines were inserted. Rigid bronchoscopy revealed no obvious source of bronchial obstruction. The child was then intubated with a 4.0 oral endotracheal tube and placed in a left lateral decubitus position. A right thoracotomy incision was made and, before the pleural space was entered, pancuronium bromide 0.5 mg and fentanyl 45 μg were administered intravenously. The ventilatory mode was changed to HFJV with 100% oxygen from spontaneous ventilation. The high-frequency jet ventilator (Instrument Development Corp. model VS 600) was set at a rate of 150 breaths/min, a driving pressure of 5 psi, and an inspiratory to expiratory ratio of 40%. Oxygen saturation was 97%. Thirty minutes after the institution of HFJV, an arterial blood sample showed pH to be 7.28, P_{O_2} 98 and P_{CO_2} 51 mm Hg. Additional pancuronium bromide 0.4 mg and fentanyl 18 μg were administered. A right middle lobe lobectomy was completed in 2 hr. HFJV was then discontinued and conventional positive pressure ventilation (PPV) employed for the first time to reexpand the right upper and lower lobes. At this time, blood O_2 saturation was 98% and an arterial blood sample showed a pH of 7.38, P_{O_2} 399 mm Hg and P_{CO_2} 35 mm Hg. When the surgery was completed, the neuromuscular blockade was reversed with

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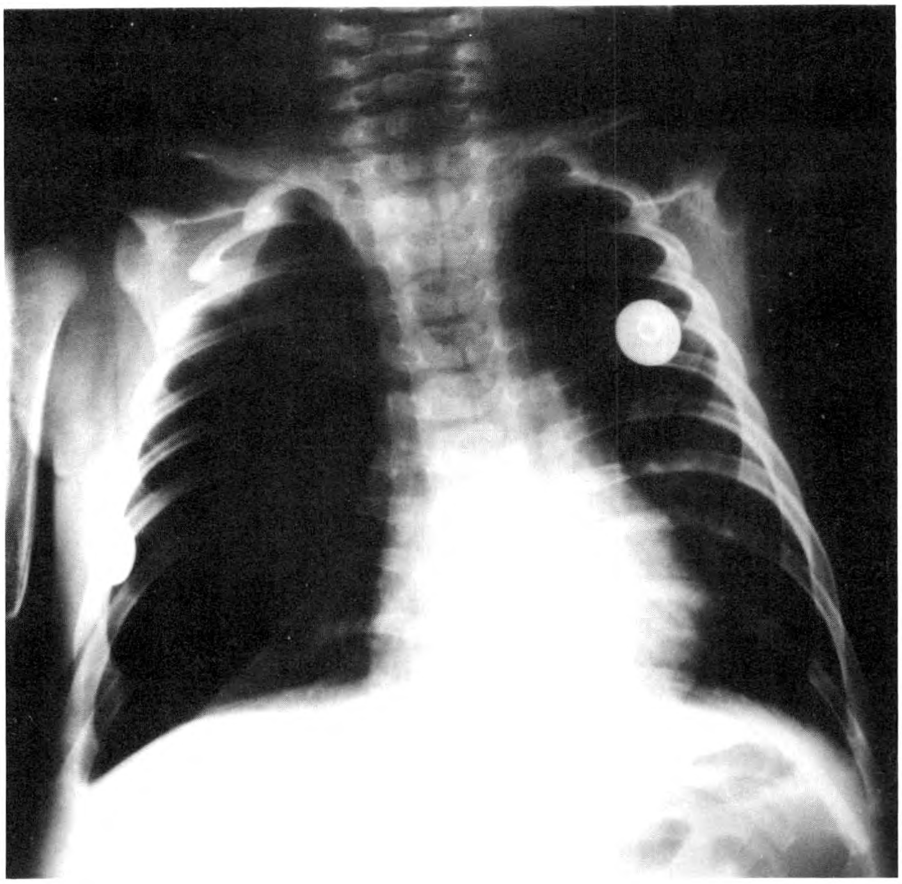

Figure 1. Chest x-ray showing a right middle lobe hyperinflation due to congenital lobar emphysema.

intravenous neostigmine 0.35 mg and glycopyrrolate 0.07 mg. Spontaneous respirations returned and the child was extubated. An uncomplicated postoperative course followed and the child was discharged home on the second postoperative day.

Discussion

Patients requiring pulmonary resections because of CLE present a number of anesthetic challenges. They may be in such respiratory distress that any premedication that might compromise respiration should be avoided. In addition to routine monitors, the possibility of hypoxemia intraoperatively is so great that monitoring of oxygen saturation with a pulse oximeter is imperative. We also prefer to use an arterial catheter to monitor blood pressure continuously and to sample blood for measurements of gas tensions and pH. Controlled PPV and inhalation of nitrous oxide should not be used while the chest is still closed so as to avoid further expansion of the emphysematous lobe and a possible tension pneumothorax.

After the pleural cavity is entered, obligatory PPV is required. We ventilated the patient using HFJV instead of conventional PPV. It has been shown that ventilation with high rates and low volumes provides fairly low mean airway pressure with minimal effect on the pulmonary and systemic circulation (2). The rate of ventilation was set at 150 breaths/min since this rate was successfully used for pulmonary lobectomy by Smith et al. (3). In our case, it was observed that either increasing driving pressure or the inspiration/expiration (I/E) ratio increased the degree of lung inflation. This is because lung volume cannot return to initial volume when respiratory cycle intervals are so short, resulting in an "auto-PEEP" effect (4). Accordingly, we adjusted the driving pressure and I/E ratio of the high-frequency jet ventilator to produce a slightly inflated and nearly motionless lung with an optimal oxygen saturation. Oxygen saturation never decreased below 90% during HFJV and the nearly motionless lung facilitated surgery. Carbon dioxide elimination during high-frequency ventilation is most strongly related to the production of frequency and tidal volume when the frequency is below about 200 breaths/min (5). Therefore, a mild respiratory acidosis observed in our patient is probably attributable to the small tidal volume secondary to the low driving pressure of jet ventilation. Nevertheless, the patient remained stable hemodynamically. Since inhalation an-

esthetics could not be administered with HFJV, fentanyl was administered intravenously.

Once the right middle lobectomy was completed, the remainder of the right lung was reexpanded by conventional PPV. The uninvolved lobes might have been mildly hypolastic, so gentle positive pressure was used (6).

Our case indicates that HFJV is an acceptable alternative during the excision of congenital lobar emphysema.

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Intraosseous Fluid Administration:
A Parenteral Alternative in Pediatric Resuscitation

Francis A. Harte, MD, Paul C. Chalmers, MD, Raymond F. Walsh, MD, Paul R. Danker, MD, and Farhan M. Sheikh, MB

A variety of routes are available for the parenteral administration of medications and fluids in pediatric patients. Despite our many technical achievements, however, intravascular access in a variety of clinical situations may be either impossible or too time consuming. Successful management of a critically ill pediatric patient often mandates rapid access to the intravascular compartment. Veins may be inaccessible, central lines in children are technically difficult, and surgical cutdowns are time consuming. In such a situation, intraosseous fluid administration remains a reliable and rapid infusion technique.

Case Report

A previously healthy 11-month-old female was admitted for treatment of multiple organ injuries sustained in a motor vehicle accident. The initial evaluation revealed right sixth and seventh rib fractures, accompanied by an ipsilateral hemopneumothorax and lung contusion, a fracture of the odontoid process of the second cervical vertebra, and a cerebral concussion. The presence of abnormal neurologic findings in her lower extremities prompted the performance of an emergency myelogram that demonstrated a total block at the level of the third thoracic vertebra. An emergency thoracic decompressive laminectomy was undertaken that showed a near total transection of the thoracic spinal cord at the T3 level.

After a week of mechanical ventilation, an elective tracheostomy was performed. At the time of surgery, a small subglottic shelf was noted above her tracheostomy site. The patient was mechanically ventilated for the ensuing 2 months in the intensive care unit. Her clinical course was complicated by the presence of a persistent pneumothorax, a staphylococcus aureus pneumonitis associated with a septic episode, recurrent bouts of tracheal obstruction due to poorly mobilized thick secretions, shifting right upper lobe and left lower lobe atelectasis, and ongoing loss of intercostal and abdominal muscle function secondary to the spinal cord injury.

As her stay in the intensive care unit lengthened, venous access became an increasingly difficult problem. In order to meet a variety of clinical needs, the patient underwent multiple peripheral percutaneous venipunctures, bilateral femoral and brachial central venous catheter placements, bilateral saphenous vein cutdowns, and placement of a right internal jugular venous line. Fortunately, she was successfully weaned from the ventilator and transferred out of the intensive care unit. On the evening before she was to be transferred from the hospital, however, the patient suffered a cardiopulmonary arrest. She was found to be apneic, pulseless, and cyanotic. Cardiopulmonary resuscitation was initiated with external cardiac chest compressions, mask ventilation with 100% oxygen, and tracheal instillation of 0.1 ml epinephrine 1:1000 and atropine sulfate 0.2 mg. A sinus bradycardia developed at a rate of 40 beats/min associated with a systolic blood pressure of 50 mm Hg and a mild metabolic acidosis.

Attempts to establish either peripheral or central venous lines were unsuccessful. Electromechanical dissociation ensued with a sinus tachycardia of 150 beats/min, unaccompanied by a detectable blood pressure by Doppler ultrasonography. Therefore bilateral intratibial catheters were inserted within 5 min under sterile conditions. Lactated Ringer's solution was administered via the left intratibial catheter and a solution of 5 mEq of 4.2% sodium of bicarbonate diluted with 10 ml of normal saline, to which 70 mg calcium chloride and 0.1 ml of 1:1000 epinephrine were added, was given through the right intraosseous

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catheter. A systolic blood pressure of 40 mm Hg resulted without notable changes in either heart rate or rhythm. Dopamine hydrochloride at 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was infused through the left intramedullary line to achieve a systolic blood pressure of 80 mm Hg. An arterial blood sample demonstrated a fully compensated mild metabolic acidosis. A left internal jugular venous line was eventually established by surgical cutdown, and the two intratibial infusion sites were discontinued. The patient recovered and was eventually transferred to a local hospital for further rehabilitation. The etiology of the cardiopulmonary arrest was believed to be respiratory obstruction from a tracheal plug.

Discussion

This case is presented to highlight the gravity of any clinical situation in which a critically ill child with difficult venous access requires emergency resuscitation. A rapid, effective method for establishing access to the general circulation can be lifesaving. Intramuscular and intratracheal routes of administration alone or in combination are limited to four emergency medications: epinephrine, lidocaine, atropine, and naloxone. Intradermal clysis, intraperitoneal infusion, and intracardiac injection of medications are either lacking in efficacy or too hazardous.

The concerns for emergency access to the general circulation in the practice of pediatrics and in pediatric anesthesia warrants early refamiliarization with the historic technique of intratibial and intrafemoral bone marrow infusions. While resurgence of the efficacy and safety of this technique has occurred among our pediatric counterparts, the anesthesia community has been slower to recall and practice this virtually forgotten technique. Although hailed in the 1940s as possibly the method of choice for fluid administration in infants with venous access problems, by the early 1950s, intraosseous infusions had faded into clinical obscurity with the advent of disposable intravenous catheters.

Techniques for intramedullary access are varied and simple. Possible sites for intraosseous infusions include the tibia, the femur, and the iliac crest in infants and small children. The preferred site of insertion is the anteromedial surface of the tibia, approximately 1–3 cm below the tibial tuberosity (1). The needle should be directed inferiorly away from the epiphyseal plate at an angle of approximately 60 degrees to the long axis of the tibia (Fig. 1). At this site, the tibial cortex is easy to penetrate and the marrow content is abundant. Eighteen-gauge spinal needles with stylets and 16- and 19-gauge butterfly needles have all been used successfully. Needle entry into the marrow cavity is accompanied by a loss of resistance, sustained erect posture of the needle without support, and/or free fluid infusion or marrow aspiration with a saline-filled syringe. The intraosseous injectate traverses the long bone marrow cavity, passing via the medullary venous channels into the nutrient and emissary veins before entering the systemic venous circulation. The long bone then serves as a noncollapsible conduit through which a variety of emergency medications and fluids can be administered.

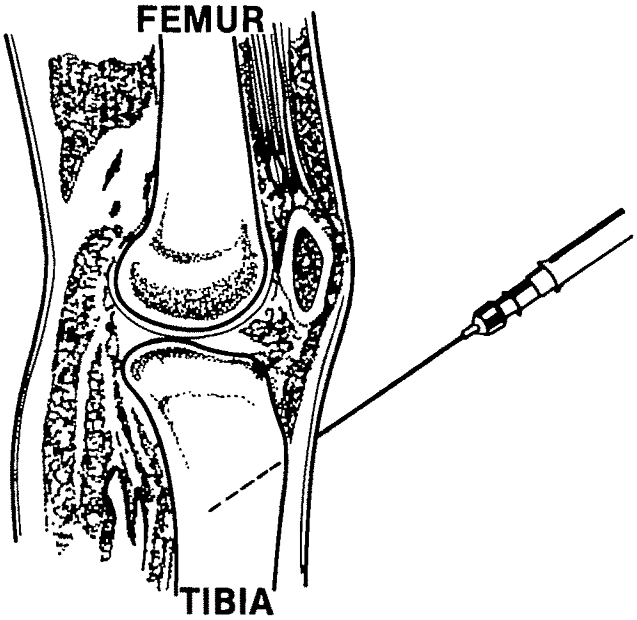

Figure 1. Site and orientation of tibial needle placement.

The efficacy of the intraosseous route for both fluid and drug administration has been supported by a multitude of pharmacodynamic and contrast agent injection studies (1–10). Infusion can be either by gravity or pressure in accordance with the patient's intravascular volume status. Gravity infusions in infant tibias typically average more than 100 ml/hr (5). The list of effectively infused fluids and substances includes whole blood, plasma, saline, lactated Ringer's solution, antibiotics, thiopental, lidocaine, radiologic contrast agents, digitalis, morphine, insulin, heparin, dilute sodium bicarbonate, calcium gluconate, and sympathomimetic amines (1,4–10).

As a result of our recent experience with emergency intraosseous infusions, we are currently stocking both 18-gauge spinal needles and 16- and 18-gauge Illinois bone marrow aspiration needles on our pediatric resuscitation carts. Although all of the aforementioned needles are effective, short bone marrow needles are preferred at our institution as they firmly

attach to the tibial cortex, thereby minimizing the risk of accidental dislodgement during resuscitation. A stylet is also helpful in removing marrow or cortical bone samples that may block free passage of the injectate. As with other invasive procedures, an aseptic technique must be adhered to. The incidence of complications with intraosseous infusions is directly related to the practitioner's technique, the duration of time the indwelling intramedullary needle is in place, and possibly the alkalinity or hypertonicity of injected fluids or medications.

Rosetti et al. (9) comprehensively reviewed complications reported in 30 clinical studies published before 1950. Of the 4359 attempted intraosseous infusions in both adults and children, 89 were unsuccessful, a failure rate of 2.1%. Technical difficulties included subperiosteal infusions, growth plate injuries, subcutaneous infiltration and/or infection, and leakage of infusion liquids back alongside the needle from the original site of cortical puncture or from prior entry sites. Of greater concern, however, was an incidence of osteomyelitis in 0.6%, or 27, of 4359 attempted intraosseous infusions (9). The development of osteomyelitis at the puncture site was related primarily to the duration of intraosseous infusions, and secondarily to the presence or absence of concurrent bacteremia, though the intramedullary infusion of hypertonic or strongly alkaline substances may also have been a factor. While continuous bone marrow infusions imply a greater risk for the development of osteomyelitis, single infusions less than 1 hr in duration have produced similar results. It is recommended that intraosseous infusions be discontinued as soon as venous access has been established.

In 1947, Heinild et al. (11) reported three cases of osteomyelitis in 25 patients, each of whom received undiluted intraosseous infusions of 5% dextrose in water. In the same year, Wallden et al. (12) reported transient decreases in medullary cellularity and edema in a rabbit model after infusion of either alkaline infusates or hypertonic solutions. Data support and prudence dictates the avoidance of hypertonic or strongly alkaline substances, as both have been implicated in the production of transient medullary histologic changes associated with an increased incidence of local infection. If infusion of alkaline substances or hypertonic solutions is contemplated, prior dilution before administration is mandatory.

Theoretical concern for release of fat or cortical bone emboli exists with this procedure, but to date neither of these potential systemic complications has been reported with intratibial infusions. The absence of documented case reports and the knowledge that children's bone marrow is relatively fat-free should place this risk in perspective.

In summary, the awareness of and ability to place an intramedullary needle is an important skill to possess for all medical practitioners involved in the management of critically ill infants and children. Familiarization with this historic clinical tool may prove lifesaving in the care of infants with difficult venous access in critical emergency situations. Despite its proved clinical efficacy, appreciation of the technical and methodologic factors that decrease the risks of untoward sequelae is important to help secure the future role of intraosseous infusions in appropriate clinical situations.

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Increases in Arterial to End-Tidal CO_2 Tension Differences after Cardiopulmonary Bypass

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The usefulness of continuous end-tidal CO_2 tension measurement in anesthetized patients is well established (1–3). End-tidal CO_2 tension is lower than arterial CO_2 tension due to dilution of the well-perfused alveolar ventilation with the alveolar dead-space ventilation. Total (physiologic) dead space is defined as the sum of anatomic and alveolar dead space (4). Alveolar dead space results from alveoli that are ventilated but not adequately perfused (4). The magnitude of this difference between the arterial and end-tidal CO_2 tension serves as a measure of alveolar dead space (4). The arterial to end-tidal CO_2 tension difference tends to be relatively small in young, healthy patients and larger in older patients with lung disease (3). Once established for any patient, the magnitude of this difference remains stable in hemodynamically stable anesthetized patients (3,4).

In our institution, we detected a widening of the arterial to end-tidal CO_2 tension difference in patients after cardiopulmonary bypass. This work was undertaken to study the arterial to end-tidal CO_2 tension difference before and after cardiopulmonary bypass in adult patients undergoing cardiac surgery.

Methods

We studied 25 patients undergoing a variety of cardiac surgical procedures that required cardiopulmonary bypass. The patients' ages ranged from 25 to 79 yr, with an average age of 65 yr. All were medicated with intramuscular morphine, scopolamine, and diazepam in doses deemed appropriate for each patient. Anesthetic induction and maintenance were tailored to the individual patient's cardiac lesion and hemodynamic responses using either a narcotic technique with fentanyl, a volatile technique with isoflurane, or a combined technique.

Simultaneous arterial and end-tidal CO_2 tensions were measured approximately 2 hr before and 30 min after cardiopulmonary bypass for elective cardiac surgery. All end-tidal CO_2 gas samples were obtained from the endotracheal tube at the elbow connector and aspirated to a mass spectrometer (System for Anesthetic and Respiratory Analysis, Allegheny Medical Technology). The mass spectrometer was self-calibrated every 2 hr with standardized gas samples. An expiratory pause of 4–8 sec assured sampling during the plateau of the expired CO_2 tension vs time curve. Blood samples for arterial CO_2 tension measurement were drawn from indwelling arterial lines into heparinized syringes. The blood samples were immediately analyzed in an operating room laboratory with a Radiometer ABL-1 blood gas analyzer, which was calibrated every 2 hr and checked twice daily with quality-control solutions (Alko reagents and a Professional Instruments tonometer). All measurements were made at 37°C and corrected to the patients' temperatures. Both prebypass and postbypass patient temperatures were always in the 34.5–37°C range during blood gas sampling.

The cardiopulmonary bypass technique involved a conventional roller pump system with a Bentley 10 bubble oxygenator and a Bentley BRC-3500 cardiotomy reservoir. Arterial line filtration was employed in all cases using a Pall EC-3840 filter. Cardiac index was kept at 2.1–2.4 L/m^2 and mean arterial pressure was maintained at 60–90 mm Hg. All patients had adequate urine output and normal acid–base balance. Minute ventilation was kept constant and normocarbia was maintained with an average prebypass CO_2 tension of 36 mm Hg and an average postbypass CO_2 tension of 42 mm Hg. In all cases, the cardiac output after bypass was equal to or greater than that before bypass as measured by the thermodilution technique with a Swan-Ganz catheter. Surgical procedures studied are listed in Table 1.

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Table 1. Operations Performed

Operation	Number of patients
Coronary artery bypass	17
Coronary artery bypass and aortic valve replacement	1
Aortic valve replacement	3
Mitral valve replacement	4
Total	25

Table 2. Arterial to End-Tidal CO_2 Tension Differences (mm Hg)

	Before bypass	After bypass
All patients	4.6 ± 2.9	11.5 ± 3.5
Smokers	4.5 ± 2.9	11.2 ± 3.7
Nonsmokers	4.6 ± 3.0	12.2 ± 2.9
Transfused patients	3.7 ± 1.8	10.9 ± 3.1
Nontransfused patients	5.5 ± 3.5	12.1 ± 3.9

Results

Temperature-corrected arterial to end-tidal CO_2 tension differences are listed in Table 2. The values obtained before cardiopulmonary bypass are in accord with the reports of other authors (3,5). The mean arterial to end-tidal CO_2 tension difference was 4.57 ± 2.86 mm Hg before cardiopulmonary bypass and 11.48 ± 3.46 mm Hg after cardiopulmonary bypass. This increase was statistically significant by both the paired Student's *t*-test ($P < 0.001$) and the nonparametric Wilcoxon signed rank test ($P < 0.001$).

Patients with histories of smoking did not have larger increases in arterial to end-tidal CO_2 tension differences than nonsmokers. Similarly, patients who received homologous blood products did not have an increase in arterial to end-tidal CO_2 tension difference above that observed in nontransfused patients. (The nontransfused patient group included those receiving autologous blood.)

Discussion

Exhaled gas is a mixture of both alveolar and dead-space ventilation. Arterial CO_2 tension is higher than end-tidal CO_2 tension because alveolar dead-space ventilation, which has a very low CO_2 tension, dilutes the CO_2 tension of well-perfused alveoli. Anything that increases the alveolar dead space will increase the arterial to end-tidal CO_2 tension difference. Patients with preexisting lung disease have greater arterial to end-tidal CO_2 tension differences than do patients without lung disease (3). Poor perfusion of adequately ventilated alveoli, such as during hypovolemia with hypotension or deliberately induced hypotension during anesthesia, results in an increase in alveolar dead space (2,6–8). General anesthesia itself increases alveolar dead space but the magnitude of this increase remains relatively constant in hemodynamically stable patients, and thus the duration of anesthesia would not explain our finding of an increased arterial to end-tidal CO_2 tension difference after bypass (3,4).

In our study, we observed an increase in cardiac output after cardiopulmonary bypass. This would tend to increase pulmonary blood flow and decrease physiologic dead space. Consequently, changes in cardiac output could not account for the increased arterial to end-tidal CO_2 tension difference.

Emboli to the systemic circulation would not be expected to increase pulmonary dead space. However, emboli to the pulmonary circulation could obstruct pulmonary capillaries, thus stopping blood flow to a ventilated region and increasing dead space. Cardiopulmonary bypass is plagued with the potential for embolization of various substances. Despite elaborate precautions to prevent embolization, many types of embolic phenomena, sometimes with disastrous consequences, have been reported (9). Not all embolization during cardiopulmonary bypass is catastrophic. In fact, considerable emphasis is placed on measures that reduce microembolization (10,11). Examples of microemboli include the following: 1) platelet or white blood cell plugs, 2) sludged red blood cells, 3) fibrin, 4) tissue fragments, 5) cloth/paper fibers, 6) plastic fragments, and 7) air.

Another explanation for the increase in dead space after total cardiopulmonary bypass relates to the lack of pulmonary blood flow during this procedure. Perhaps some pulmonary capillaries do not reopen immediately after the cardiopulmonary bypass. The various pulmonary vascular beds probably have different critical opening pressures.

In summary, this study demonstrates an increased pulmonary dead space following cardiopulmonary bypass as measured by an increased arterial to end-tidal CO_2 tension difference. Some possible reasons for this increase in physiologic deadspace have been presented. When capnography is used during anesthesia, it is important to maintain lower levels of end-tidal CO_2 after cardiopulmonary bypass in order to achieve normocarbia.

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Letters to the Editor

Preoperative Anisocoria from a Scopolamine Patch

To the Editor:

A healthy, 27-yr-old woman (60 kg) was scheduled for an elective outpatient tubal ligation. Her medical history was unremarkable. Laboratory data were normal. Physical examination was normal except for a dilated, 6-mm left pupil that failed to contract with light or accommodation. Neurologic examination was normal.

The patient was questioned regarding the use of any ophthalmic medications, and although she denied the use of any medication that could dilate the pupil, she did recall that 1 week ago she had placed a scopolamine patch behind her left ear to prevent motion sickness during a sailing trip. Not only had she not removed it, she had, in fact, "played" with it nervously in the waiting room. The patch was removed and over the next 2 hr her pupil returned to normal. Anesthesia and surgery then proceeded uneventfully, and the patient was discharged in good condition. Postoperative follow-up revealed no problems.

Transdermal scopolamine is used to prevent motion sickness. (1) The patch contains 1.5 mg of scopolamine and is programmed to deliver 0.5 mg of scopolamine over 72 hr. According to the manufacturer's recommendations scopolamine patches are to be removed after 3 days' use, but the scopolamine may still be active for up to 2 weeks and it is possible that the patient may forget the patch has been applied (2,3).

If absorption of scopolamine was the cause of the pupillary dilation in this case, bilateral dilated pupils would have been observed. The unilateral mydriasis was most probably due to direct contamination of the eye by manipulation of the patch and subsequent transfer by the fingers to the eye. The patient was unaware of potential ophthalmic complications from the use of the patches despite the fact that the package insert describes temporary blurring of vision and dilation of pupils due to transfer of the drug from fingers to eyes. Over 90% of unilateral dilated pupils occur on the same side as the patch (2).

The diagnosis of a pharmcologically dilated pupil can be confirmed with the instillation of 0.5–1% pilocarpine hydrochloride ophthalmic solution into the affected eye. Failure of the pupillary sphincter to constrict after pilocarpine signifies a problem located within the eye, such as a drug-induced mydriasis (4).

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Sudden Hypotension Associated with Midazolam and Sufentanil

To the Editors:

Spiess et al. (1) described four cases of sudden hypotension on induction of anesthesia with high-dose sufentanil. They noted that all four patients also had intravenous lorazepam during induction. The authors concluded that benzodiazepine–narcotic interaction was a possible cause of the hypotension, and they also noted that diazepam–sufentanil as a combination has been associated with direct myocardial depression and a decrease in preload.

We would like to report hypotension in a patient in whom sufentanil was used for induction of anesthesia after preoperative intramuscular midazolam. The patient was a 60-kg, 50-yr-old man with hypertension and aortic insufficiency who was scheduled for aortic valve replacement. Medical treatment included clonidine, captopril, and furosemide.

Preoperative medication consisted of midazolam, 5 mg intramuscularly. After 0.3 mg glycopyrrolate intravenously, anesthesia was induced with 150 μg (2.5 μg/kg) sufentanil over 4 min. The blood pressure decreased from 130/60 to 76/40 mm Hg and the pulse from 90 to 55 beats/min. Atropine, 0.4 mg, and ephedrine, 10 mg intravenously, had no

effect. Repeated doses of 0.4 mg atropine and ephedrine, 10 mg intravenously increased the blood pressure to 110/60 mm Hg and the pulse to 80 beats/min. No further vasopressors were needed before going on cardiopulmonary bypass.

There have been conflicting reports in the literature concerning the use of IV midazolam in conjunction with fentanyl anesthesia. Massant et al. (2) found only a 17% decrease in mean arterial blood pressure (MABP), a 9% decrease in pulse, and a slight increase in endocardial viability ratio in eight patients. Heikkila et al. (3), however, found a 24–32% decrease in MABP in 18 patients.

Although more controlled studies are needed, our experience in this case is certainly consistent with that of Spiess et al. and suggests that any benzodiazepine in combination with sufentanil may predispose patients to sudden hypotension.

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Caudal Anesthesia and Cardiovascular Collapse in an Infant

To the Editor:

We read with interest the account by Matsumiya et al. (1) of a case of cardiovascular collapse in a healthy infant given a caudal anesthetic. We disagree, however, with the authors' analysis of the cause-and-effect relationship between the caudal block and cardiovascular collapse.

The article noted that anesthesia was maintained by mask using halothane 1.5%, nitrous oxide 67%, and oxygen 33%, while the child was turned into the lateral position for induction of caudal anesthesia. After the infant was returned to the supine position, systolic blood pressure decreased from 70 to 30 mm Hg, heart rate decreased from 180 to 60 beats/min, respirations became gasping, and spotty cyanosis developed.

The authors attribute the collapse to intravascular injection of the lidocaine-epinephrine solution. We suggest an alternative explanation: the infant was hypoventilated for a significant period of time, with hypercarbia, hypoxia, and a relative overdose of halothane playing a significant role in subsequent cardiovascular collapse. Our explanation is supported by the arterial blood gas levels obtained within 5 min of collapse: pH 7.25, $Paco_2$ 51 mm Hg, Pao_2 355 mm Hg, and base excess −6 mEq/L. A $Paco_2$ of 51 mm Hg after 5 min of hyperventilation with 100% oxygen during resuscitation suggests a protracted period of hypoventilation prior to the cardiovascular collapse.

The dose of lidocaine administered to this child was 8.3 mg/kg. One of the authors of the present paper (1) published an article in 1977 regarding the safe dosage of lidocaine for caudal anesthesia in infants and children (2), using lidocaine doses up to 9.4 mg/kg with epinephrine 1:200,000 in a technique similar to that reported in the present article. The plasma levels of lidocaine reported in this infant 15 min, 2 hr, and 3 hr, after cardiovascular collapse show a decay curve midway between that of intravenous lidocaine in children as reported by Finholt et al. (3) and caudal lidocaine as reported by Yaster et al. (4) The absence of motor or sensory blockade suggests that all the local anesthetic did not go into the caudal space; however, the plasma levels of lidocaine do not support the authors' contention that it all went in the intravascular compartment. It is therefore unclear what part lidocaine had to play in the collapse.

Finally, Matsumiya et al. conclude that the inclusion of epinephrine in lidocaine solutions may be harmful and certainly is not protective against cardiac toxicity caused by intravascular injection of lidocaine. However, it is interesting to note that the authors used a larger dose of epinephrine (52 μg) in resuscitation of this infant than the 22.5 μg contained in the lidocaine–epinephrine solution, condemned as having caused the cardiovascular collapse. The authors, themselves, remark on the contradiction implied in stating that a drug that caused cardiovascular collapse was also instrumental in the reversal of that collapse seconds later.

We believe lidocaine may have played a minor role in the cardiovascular collapse of this infant but suggest that the major causative factors were airway management, hypoxia, hypercarbia, and halothane. In addition, we feel that more studies are needed before reaching conclusions that epinephrine should not be added to caudal lidocaine.

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Kinetics of Epidural Morphine

To the Editor:

We read with interest the article by Durant and Yaksh entitled "Distribution in cerebrospinal fluid, blood, and lymph of epidurally injected morphine and inulin in dogs" (*Anesthesia and Analgesia*, 1986;65:583–92). We are concerned, however, about the methods they used to measure levels of morphine in plasma. The dogs were given ^{3}H-labeled morphine (2 mg) and the morphine level in plasma was calculated on the basis of the amount of radioactivity. Have the authors overlooked the fact that morphine is rapidly conjugated in the liver and that the plasma radioactivity in their experiments therefore represents the sum of unconjugated and conjugated morphine?

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In Response:

We agree with Drs. Andersen and Christensen that plasma radioactivity in our experiment reflects the sum of unconjugated and conjugated morphine. In dogs, morphine conjugates, primarily morphine glucuronide, account for more than 90% of the radioactivity in plasma 2 hr after intravenous injection (1). Similar data have been reported in rabbits (2). As interesting, however, is the relevance of conjugates in the cerebrospinal fluid (CSF). In some mammals, conjugating enzymes (particularly leading to sulfation) occur not only in the liver, but also in the CNS (3,4). Therefore, the CSF data also potentially reflect unchanged and conjugated morphine. Indeed, we have previously speculated that the high dose effects of spinally administered morphine may result from this central conversion (5). To our knowledge, conjugation in the CNS has not been quantitated in dogs (or in most species for that matter). Nevertheless, it is worthy of mention and further investigations would be valuable.

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Pulse Monitoring without ECG Is Potentially Hazardous

To the Editor:

In a recent communication, Daniels and Rosen (1) point out the cost-effectiveness of pulse monitoring when test-dosing obstetric epidural catheters with epinephrine-containing local anesthetics. However, in stating that ECG monitors are expensive and large, they miss the point of the previous communication of Diehl and Loeser (2), to which they refer. The MicroCor ECG monitor (MicroCor Inc., Salt Lake City UT) is extremely compact and inexpensive.

I believe it is fallacious to equate pulse monitoring with ECG monitoring. To inject arrhythmogenic substances without being able to conclusively determine rhythm is potentially hazardous to the patient; it carries malpractice implications as well. I know I am not unique in having had the experience of listening to an apparently normal sinus rhythm while the ECG monitor demonstrated obvious bigeminy.

The same standards of care that are present in the operating rooms must exist in the delivery area.

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Removing the Macrame from Monitoring Devices

To the Editor:

Over the last few years, anesthesia personnel have seen an explosive increase in the number of monitoring devices being used in the operating room. With each monitoring addition has also come the necessary cable or tubing required to carry the electrical or gas data to the monitoring device. A recent article has attempted to address the problem of the maze that develops at the rear of the anesthesia machine (1). This letter's focus is on the forward entanglement.

After spending several frustrating moments untangling the maze of cable macrame, I decided to devise a better way to organize this small annoyance. Two standard lengths of plastic disposable adult circuit hoses were split down their entire length with a scalpel. The 22-mm end couplings were removed to allow only the corrugated portions of the circuit to remain. The monitoring cables and tubing were then placed inside the hoses, leaving a generous length available at the distal end to allow the tubes, cables, and electrode wires to be properly applied to the patient and anesthesia Y-piece. The cable umbilicus that is formed allows flexibility in monitoring while still corralling the potential macrame and generally appealing to most anesthesia personnel's obsessive–compulsive nature.

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Anesthetic Management of Mediastinal Masses—Again

To the Editor:

The case report by Northrip et al. (1) describes another anesthesia-associated death in a patient with a large, anterior mediastinal mass. Their patient, an 11-yr old girl, had all the symptoms and signs that presage danger. Posture-related dyspnea is an ominous sign of unstable lower airway dynamics, and anesthetic drugs can precipitate complete airway obstruction unrelievable by tracheal intubation, as they describe. In the presence of superior vena cava syndrome (SVCS) catastrophic deterioration may attend the induction of anesthesia, especially if a head-up tilt is not maintained, and this they also describe. Even if a large lower-limb venous cannula is in place, it can be difficult for the surgeon to control, and the anesthesiologist to replace, blood lost from the extensive hemorrhage that will accompany surgery in SVCS. Autopsy was not performed, but I believe the presence of a murmur signalled pulmonary artery compression compounding the hemodynamic and respiratory embarassment already detailed (2).

Recognition of any of the above should be a clear warning to avoid surgery other than lymph node biopsy using local anesthetic and to avoid sedative drugs or airway manipulations except for resuscitation if the situation becomes desperate. Acknowledging the dangers of anesthesia and surgery, as evidenced by successive reports of similar cases and near-misses, oncologists, surgeons, and anesthesiologists must pause in the search for a definitive histologic diagnosis and institute urgent empirical therapy, usually of radiation and corticosteroids. Anxiety that thereby ultimate biopsy tissue will be distorted and uninterpretable should be viewed against the dismal results of immediate attempts to obtain tissue. The contention by Neuman et al. that a tissue diagnosis is mandatory before radiation therapy can be instituted is incorrect (3). Superior vena cava syndrome, postural dyspnea, or both, urgently warrant the relief usually afforded by empirical treatment. Only in the newborn is respiratory obstruction associated with a mediastinal mass likely to be due to a benign lesion such as a cyst or esophageal duplication.

Since Mackie and Watson (2) reviewed the literature in 1984, six further case reports including three deaths in children have been published, so the problems of airway obstruction and SVCS related to a mediastinal mass, though rarely seen by an individual anesthesiologist, continue to appear (1,3–5). It is to be hoped that the publishing of these case histories will lead to recognition of the dangers these patients present, as we now all recognize the significance of other rare disorders, such as malignant hyperpyrexia. The importance of initiating radiotherapy to control the SVCS and airway obstruction cannot be overstressed (6).

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2. Mackie AM, Watson CB. Anaesthesia and mediastinal masses. Anaesthesia 1984;39:899–903.
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Book Reviews

Anesthesia and Uncommon Pediatric Diseases

Jordan Katz and David J. Steward, eds. Philadelphia: W. B. Saunders, 1987, 560 pp, $65.00.

Anesthesiologists who care for pediatric patients have long needed an authoritative source on the more unusual pediatric diseases and syndromes written from an anesthesiologist's perspective. To fill this need, the editors have assembled as contributors respected authorities from the United States, Canada, and the United Kingdom.

The first two of the 18 chapters provide the reader with concise yet complete and current information pertinent to anesthetic management on aspects of anatomy, physiology, and pharmacology in infants and children. The remaining chapters encompass major organ system diseases or topics with more general headings, such as infectious disease, head and neck syndromes, and orthopedic diseases.

As with any project of this magnitude and scope, there are strengths and weaknesses; however, the former far outweigh the latter. In selecting authors from a wide geographic distribution, the editors avoided the provincialism that can result when contributors are selected from a single institution or confined geographic region. Differences in style and format from chapter to chapter are noted but are not particularly disturbing. Reference format varies.

The title suggests that the topic is "uncommon" disease; however, I noted some inconsistency and a lack of criteria for selection of "uncommon disease." However, inclusion of a disease that may be regular fare for a pediatric anesthesiologist may indeed be an uncommon disease in the general population, and authors are given latitude in this regard.

The reader is provided with tables, graphs, and illustrations, which are particularly valuable in those chapters dealing with the nearly inexhaustible list of "pediatric syndromes," whether cardiac, craniofacial, or metabolic. Syndromes are indexed for quick reference, and bibliographies are extensive and up-to-date. Most chapters are well footnoted.

There may be a tendency to compare the book to *Anesthesia and Uncommon Disease* (Katz, Benumof, and Kadis. W. B. Saunders, 1981). However, *Anesthesia and Uncommon Pediatric Disease* is by no means a revision of the adult book, although they share similar titles, one editor, and one contributing author. Some overlap in subject matter inevitably occurs; where it does, the approach in *Anesthesia and Uncommon Pediatric Diseases* is from a uniquely pediatric perspective, with appropriate emphasis on genetics, embryology, and development. The management prescriptions are concise and well organized. The authors not only evidence excellent theoretical command of the subject material but project the confidence and practicality of experienced practitioners with firsthand experience to complement their scholarship.

This volume is a significant contribution to the anesthesia literature. It brings together important information and makes management suggestions for the "bewildering array" of diseases and syndromes in the pediatric population. As such it will prove an important reference for all students of the specialty whether in training or in practice.

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Anaesthesia Review 3

Leon Kaufman, ed., New York: Churchill Livingstone, 1985, 216 pp, $22.00.

This book is a continuation of two earlier series that review current literature relevant to clinical practice. A distinguished group of anesthetists from the United Kingdom has written 17 interesting chapters on problems, controversies, and newer concepts confronting the anesthesiologist. Published in 1985, sections are included on drugs and various diseases as they affect the course of anesthesia.

Specific well-written chapters that warrant mention include a historical discussion of muscle relaxant development as it leads to the release of the new short-acting drugs. Complications and risks associated with blood transfusion therapy are extensively reviewed, with comments on the clinical use of modified hemoglobin solutions, colloid volume expanders, and the new perfluorochemical synthetic blood substitutes. One chapter deals with the physiologic

and metabolic assessment of normal brain function, commenting on different techniques for electroencephalographic and evoked potential analysis. The virtues of formerly and presently available inhalational anesthetics are described, with criteria for appraising the different agents, including the possibility of improving their characteristics. Interesting insights are discussed that may have been lost with the disappearance of certain agents from clinical practice. In addition, there is a useful review of opioid receptors and their pharmacologic importance.

Despite the interesting nature of this book, it includes out-of-date material. For instance, the section on acquired immunodeficiency syndrome (AIDS) in the blood transfusion section raises the prospect of a screening test for AIDS that is currently available. Also, clinical practices in the United Kingdom may differ from those in the United States. The removal of the intravenous steroid anesthetic althesin from clinical use is of little interest on this continent. Nonetheless, these are minor criticisms of a valuable text.

With the sheer bulk of published literature in medicine, it is often difficult to assess what is important to continuing medical education for the maintenance of high standards of anesthesia practice. Although the text is already 2 years old, Kaufman provides an interesting and concise update of relevant topics. *Anaesthesia Review 3* is easy to read and provides a refreshing approach to newer concepts as well as reexamining some older concepts in anesthesia from a historical perspective. I would recommend this book to both practitioners and residents in training looking for something to span the gap between material in journals and textbooks.

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Anesthetic Consideration for Craniotomy in Awake Patients

George P. Varkey, ed. Boston: Little Brown and Co., 1986, 190 pp, $53.00.

The subject covered in this book, which is volume 24, number 3 in the International Anesthesia Clinics series, is one which has been given only limited coverage by the available texts on neurosurgical anesthesia. Perhaps this gap has resulted because there are so few groups which perform seizure surgery on the awake patient.

The book is a multi-authored text consisting of 11 chapters; it is well-written with little redundancy or clashes in style. The first two chapters are complete reprints of texts delivered to the annual meeting of the members of the International Anesthesia Research Society in 1953. These two chapters deal with first the surgical and then the anesthetic considerations employing both regional and general anesthesia for craniotomy and cortical exploration. These presentations were prepared by Drs. Penfield and Pasquet and were published a year later in *Current Researches in Anesthesia and Analgesia*. Although these two chapters describe work of two pioneers in the field and make entertaining reading, a more concise summary of their techniques, particularly those aspects which remain pertinent today, would have been preferred.

The next seven chapters review the different classes of epilepsy, as well as the medical and surgical therapy of seizure disorders. Overall, these chapters are well-prepared. The chapter on medical management of epilepsy and theoretical basis for surgical therapy is particularly good, although a discussion on the use of general anesthesia in status epilepticus would have been beneficial. In the chapter on resection of intracranial lesions under local anesthesia, the author evidences a bias against general anesthesia for craniotomy, particularly in the elderly, even when no need exists to have the patient awake. This attitude is essentially a "they do better" rationale, with the author admitting that his observations are not based on solid scientific evidence.

The final two chapters deal with actual anesthetic management, first at the University of Western Ontario and second at the Montreal Neurological Hospital and Institute. These two chapters do a very good job of describing the difficulties which can be associated with doing such lengthy and meticulous procedures under local anesthesia. Techniques for developing and maintaining the patients confidence are nicely presented.

The management of the patient who becomes uncooperative and must be given a general anesthetic with the head already open sounds frightening but is approached in a logical fashion, although the potential use of a fiberoptic laryngoscope is not discussed. Also omitted are considerations or even speculation on the role that some of the newer drugs may play in this field. Fentanyl and droperidol are discussed in depth. However, the newer narcotics, benzodiazepines, and the opioid agonist–antagonist drugs, which may well be useful in this type of surgery, are not adequately discussed. A more glaring omission is the failure to discuss anesthetic considerations for procedures such as percutaneous cordotomy, cryogenic thalamotomy, percutaneous trigeminal rhizolysis, or cryogenic hypophysectomy. These procedures as well as others are mentioned in the introduction but are not covered in the text. The book can also be criticized for the quality of the illustrations. The photographs did not reproduce well, and although the prepared diagrams are good, they are too few in number. The references also are too few; the number of references for each chapter ranges from six to 28, with very few citations after 1980. On the plus side, however, is a very good index.

This book will be useful to those who are involved in the care of patients who will be awake during craniotomy. Anesthesiologists who are interested in neurosurgical anesthesia or who desire a comprehensive library in neuroanesthesia may also find this book of interest. The authors

recommend strongly that the sedation techniques for craniotomy in awake patients should only be employed by those who have had previous training and instruction in these techniques. From some of the problems they have encountered, it is easy to understand why they make that recommendation.

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Anesthesia and ENT Surgery: Volume 9, Contemporary Anesthesia Practice

Burnell R. Brown Jr and Stanley W. Coulthard, eds. Philadelphia: F. A. Davis Co., 1987, 173 pp, $30.00.

Anesthesia for ENT surgery historically has been one of the most challenging specialties in the discipline. As with many types of surgery, the technological explosion of the last two decades has made possible new ENT procedures that our predecessors could hardly anticipate. To accomodate these more aggressive surgical procedures, the anesthesiologist caring for ENT patients has been challenged to provide creative and safe techniques for sharing the airway with the surgeon.

Anesthesia and ENT Surgery is the ninth volume in the *Contemporary Anesthesia Practice* series edited by Burnell R. Brown Jr. The purpose of the CAP series is to present new developments in clinical anesthesia in an accessible format for the practicing anesthesiologist. Whereas much of what is covered in this text cannot be considered new, it nevertheless fills part of the void in the current literature of ENT anesthesia. The editors did not intend for the book to be a comprehensive text, and at 166 pages it is not. Readers who desire an extensive overview of ENT anesthesia must still consult many sources. However, the material chosen for inclusion in this volume is generally well-presented with few factual or typographical errors.

The book is divided into four sections: pharmacology, airway problems, ENT surgical procedures and anesthesia, and ambulatory surgery. Included in the pharmacology section are two chapters which are some of the most comprehensive reviews in the current literature on the subjects of catecholamine and cocaine use in surgery. The catecholamine chapter should be mandatory reading for residents. It includes a concise summary of recommendations regarding the clinical use of catecholamines with anesthetic drugs.

The second section, dealing with airway problems, includes two chapters that overlap in their discussions of airway management. The chapter by Prust and Calkins features an orderly presentation of the causes of upper airway obstruction in adults, as well as a good discussion of airway management. The description of Venturi ventilation, however, is too brief and inadequately covers hazards and their avoidance. The reader will need to consult other reviews before attempting this technique. Stehling's chapter on pediatric airway management is an appropriately concise review for a text of this scope. It contains a nice discussion of croup and epiglottitis, as well as an excellent plan of management for a child with acute respiratory distress.

The third section of the text, entitled "ENT Surgical Procedures and Anesthesia," is where this volume's limited scope leaves the reader somewhat disappointed. This "how I do it" section begins with a chapter authored by a surgeon raising few useful points that wouldn't be known to most anesthesiologists. The techniques described could be improved by the use of newer drugs with fewer undesirable side effects. The chapter on laser surgery is the first substantive new material included in the volume. It is concise and includes an excellent description of endotracheal tube preparation and a protocol for management of airway fires. As in earlier chapters, however, there is a place for a more extensive discussion of jet ventilation. The section concludes with four descriptions of anesthesia for tonsillectomy and adenoidectomy by anesthesiologists from different medical centers. Again there is nothing new here, but one can compare techniques if desired.

In summary, this volume in the CAP series is a welcome addition to the limited field of textbooks covering the current practice of ENT anesthesia and surgery. The scope of the text will frustrate those who desire a comprehensive discussion of the subject, but the areas selected for inclusion are generally thoroughly reviewed and well-written. The book would make a nice addition to teaching libraries and to the library of the practicing anesthesiologist who wants to review airway management or to become familiar with laser microlaryngeal surgery.

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AIDS

Jay E. Menitove and Jerry Kolins, eds. Arlington, VA: American Association of Blood Banks, 1986, 106 pp.

The lay press has alarmed the American people by warning us of a plague in our midst, an epidemic to rival those that ravaged Europe in the Middle Ages. Strong stuff! Those plagues depopulated village, town, and city and killed one-third to one-half the population of the continent. Are we being herded toward Armageddon by the four horsemen of the Apocalypse, ravaging the countryside, with their newly-acquired name, AIDS? Perhaps. Or, are the periodicals merely pandering to the American love of exaggeration and hyperbole, more interested in selling papers than they are in disseminating fact? Anesthesiologists, as do other physicians, look for knowledge about the acquired immu-

nodeficiency syndrome, and specifically, for help in caring for their patients, and protecting themselves from the contagion. Distillation of hysteria should leave a core of truth; but where to find it?

Fortunately, the American Association of Blood Banks has produced another little jewel in their series of publications, this one entitled simply *AIDS*. Its 106 pages consist of a series of papers presented at the AIDS Technical Workshop in San Francisco in November 1986. The book suffers from the defects of a multi-authored work in that repetition of basic facts is common, but "repetition is the mother of knowledge" and never becomes obtrusive. Then too, the book is not directed at anesthesiologists, but the fundamentals of etiology, clinical course, prognosis, methods of transmission, risks to contacts, and health care personnel, are spelled out in detail sufficient enough to give any physician a firm foundation for understanding this complex, revolutionary, and fascinating disease.

The writing is clear and concise, and good editing has minimized interauthor variability. The type is easy to read, and the topics flow logically one to the other. Each chapter is well-referenced, and the book provides a basic and current bibliography in the field.

The public has reason to be fearful. It took five years to report the first thousand cases of AIDS but only six months to find the second thousand, and the pace of reporting continues unabated. We do not know all the details of AIDS, for its incubation period may be as long as seven years, and the disease was first definitely discovered only in 1981. The ELISA test for the antibodies to the causative virus is notoriously unreliable, as only 33% of "positive values" are truly positive. Thus the meaning of this screening test is obscure, its importance unclear, and its prognostic significance moot.

The editors are blood bankers and are happy to point out the great [but not absolute] safety of blood available for transfusion. Recommendations to limit spread of the disease are documented. Unfortunately, specific precautions for health care workers are not listed, and would have increased the value of this book. Nevertheless, basic facts are there, presented clearly and without histrionics. This book represents an excellent primer in AIDS for the concerned physician.

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Books Received

Receipt of the following books from their publishers is acknowledged with thanks. Selected books from this list will be reviewed in the future.

Adams AP, Hewitt PB, Rogers MC. Emergency Anaesthesia. Philadelphia: WB Saunders, 1986, 372 pp, $25.95.

Camplan TV, Turner JM. Neurosurgical Anaesthesia and Intensive Care, 2nd ed. Stoneham, MA: Butterworths, 1986, 323 pp, $39.95.

Felts JA. Anesthesia and the Geriatric Patient (Vol 4, No 4, Oct 1986 of the Clinics in Anaesthesiology). Philadelphia, PA: WB Saunders Co., 1986, 1050 pp.

Jayson MY, ed. The Lumbar Spine and Back Pain. New York: Churchill Livingstone. 1987, 463 pp, $98.00.

Kirby RR, Brown DL, eds. Anesthesia for Trauma, Vol 25, No 1 of International Anesthesiology Clinics. Boston, MA: Little Brown Co., spring 1987, 215 pp, $24.00.

Petiss JD, Fineberg KS, Kroll DA, Collins V. Anesthesiology and the Law. Washington, DC: Health Admin Press, 1983, 397 pp.

Robertson WO. Medical Malpractice: A Preventive Approach. Seattle, WA: Univ of Washington Press, 1985, 212 pp.

Simpson PJ, Goodman NW. 600 MCQs in Anesthesia: Clinical Practice. New York: Churchill Livingstone, 1987, 232 pp, $12.50.

Stanley TH, Petty WC, eds. Anesthesia, the Heart and the Vascular System. Boston: Martinus Nijhoff Publishers, 1987, 226 pp, $62.00.

A Guide for Authors

Manuscripts should be sent to:

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- ☐ Letters to the editor, less than 300 words in length, include brief constructive comments concerning previously published articles or brief notations of general interest. The manuscripts must be double spaced, and a title and three copies must be provided.
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2. *Personal author(s) books and monographs*
   Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974:406.
3. *Chapter in a book*
   Weinstein L, Swartz, NM. Pathogenic properties of invading microorganisms. In: Sodeman WA, Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457–72.

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Legends for Illustration

☐ Type legends for illustrations double spaced starting on a separate page, with arabic numerals corresponding to the illustrations.

☐ When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend.

Abbreviations

☐ The full term for which an abbreviation stands should precede its first use in the text unless it is a standard unit of measurement. Avoid abbreviations in the title.

☐ Do not synthesize new or unusual abbreviations. When many abbreviations are used, include all in a box of definitions at the start of the article.

☐ Consult the following sources for abbreviations:

1. CBE Style Manual Committee. Council of Biology Editors style manual: a guide for authors, editors, and publishers in the biological sciences. 4th ed. Arlington, Virginia: Council of Biology Editors, 1978; and
2. O'Connor M, Woodford FP. Writing scientific papers in English: an ELSE-Ciba Foundation guide for authors. Amsterdam: Elsevier-Excerpta Medica, 1975.

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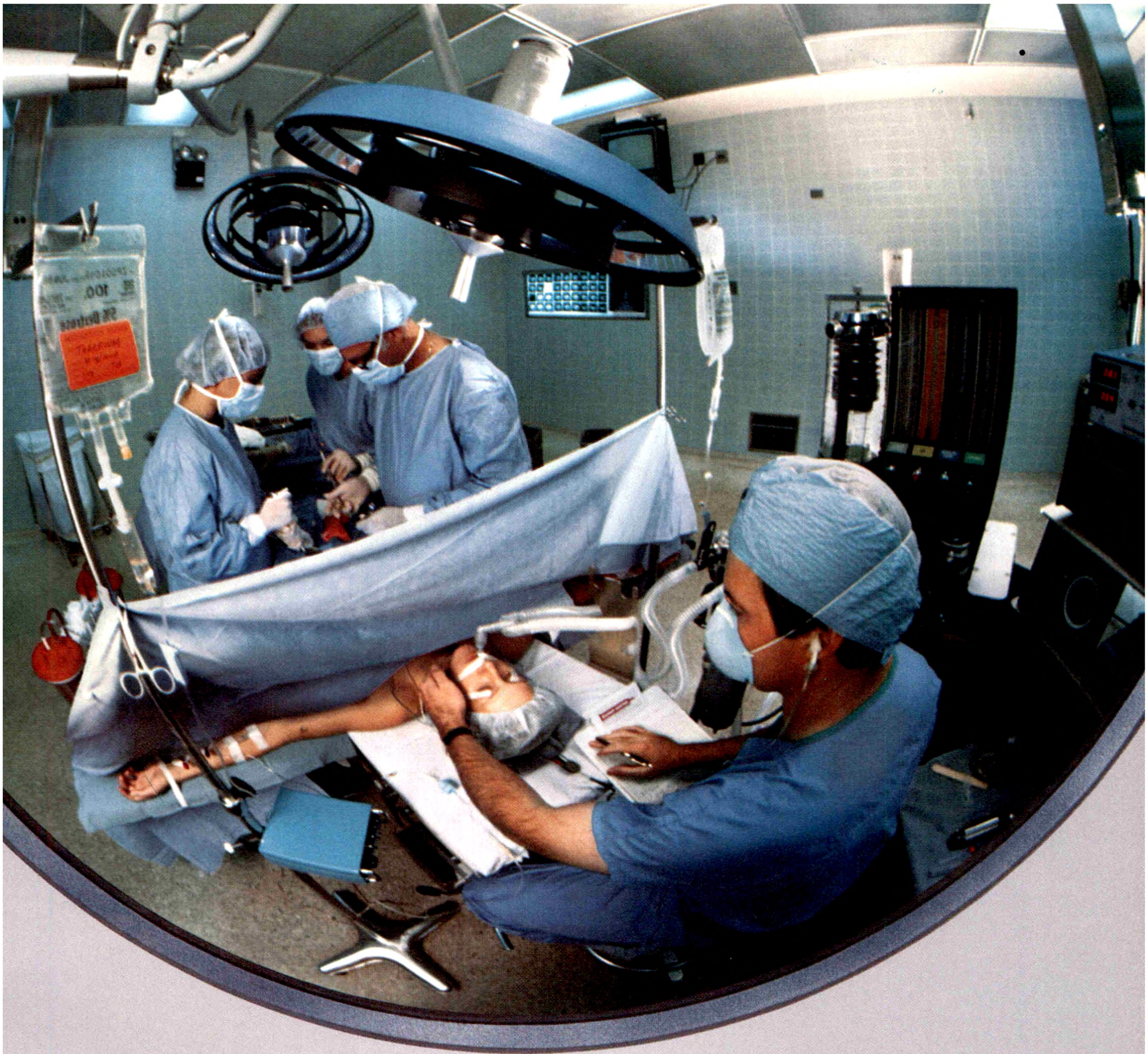


NEW...CONTINUOUS INFUSION

Smoother control

Continuous infusion represents a significant advance in the delivery of nondepolarizing neuromuscular blockade. Continuous infusion of TRACRIUM® (atracurium besylate) offers advantages over repeated bolus doses of intermediate or long-acting neuromuscular blockers for maintaining smoother, continuous muscle relaxation in procedures ranging from 30 minutes to several hours.

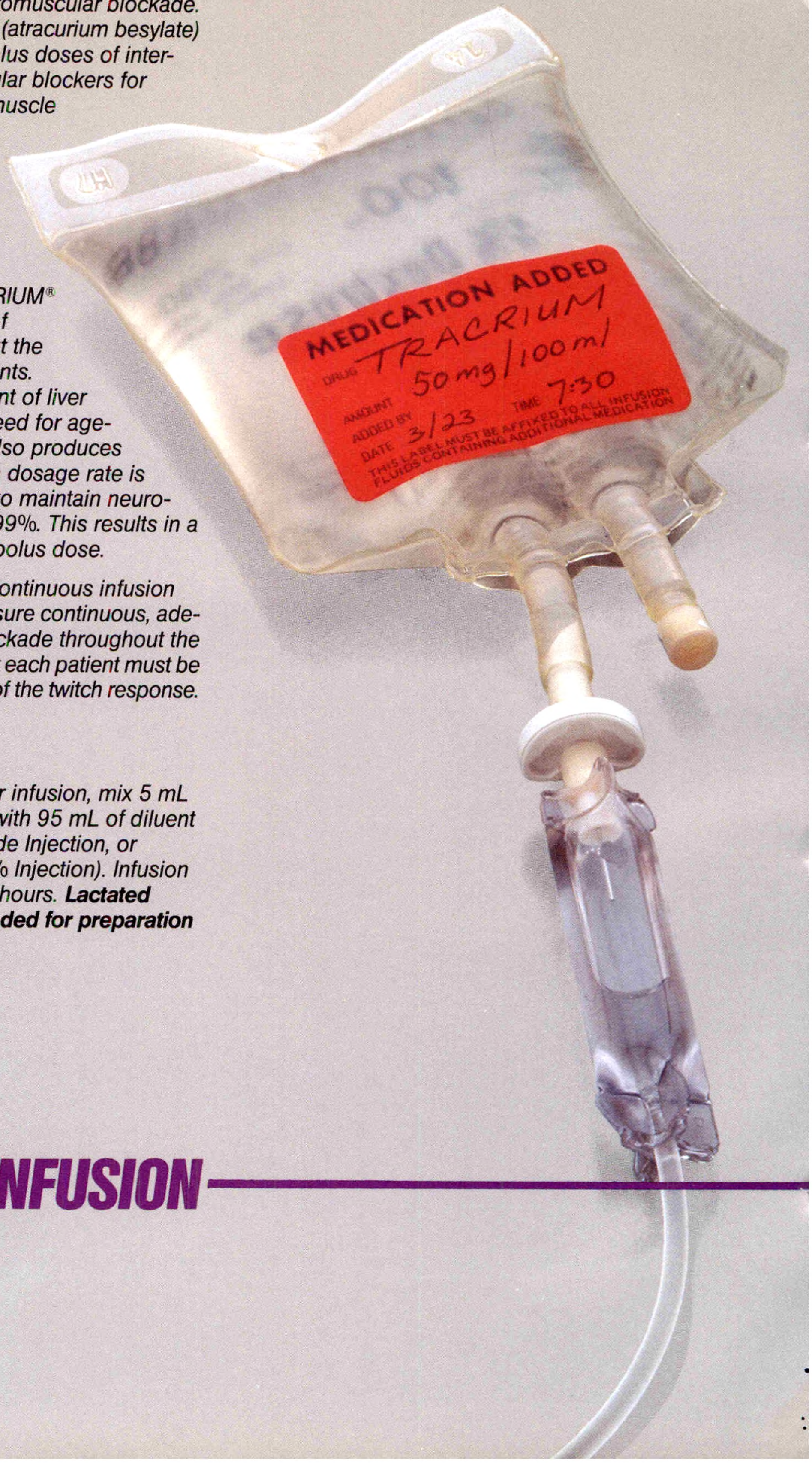
Unique metabolism—ideal for infusion

The intermediate duration of TRACRIUM® allows rapid and accurate titration of neuromuscular blockade throughout the procedure, unlike longer-acting agents. The unique metabolism, independent of liver or kidney function, eliminates the need for age-related adjustments. TRACRIUM® also produces no cumulative effects when infusion dosage rate is administered and monitored so as to maintain neuromuscular block between 89% and 99%. This results in a recovery profile similar to an initial bolus dose.

Patients receiving TRACRIUM® by continuous infusion should be monitored carefully to assure continuous, adequate control of neuromuscular blockade throughout the procedure. Infusion requirements for each patient must be individualized, based on monitoring of the twitch response.

Convenient to prepare

To prepare a 0.5 mg/mL solution for infusion, mix 5 mL TRACRIUM® (atracurium besylate) with 95 mL of diluent (Dextrose 5%, 0.9% Sodium Chloride Injection, or Dextrose 5%/Sodium Chloride 0.9% Injection). Infusion solutions should be used within 24 hours. ***Lactated Ringers Injection is not recommended for preparation of TRACRIUM® infusion solutions.***



NEW
CONTINUOUS INFUSION

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

TRACRIUM® (atracurium besylate)

Predictable recovery

Spontaneous recovery following discontinuation of TRACRIUM® infusion may be expected to proceed at the same predictable rate, comparable to that following an initial bolus dose.

Guidelines for administration

Initial loading dose: *Administer an initial bolus dose of 0.3-0.5 mg/kg (approximately 21-35 mg in a 70 kg adult).*

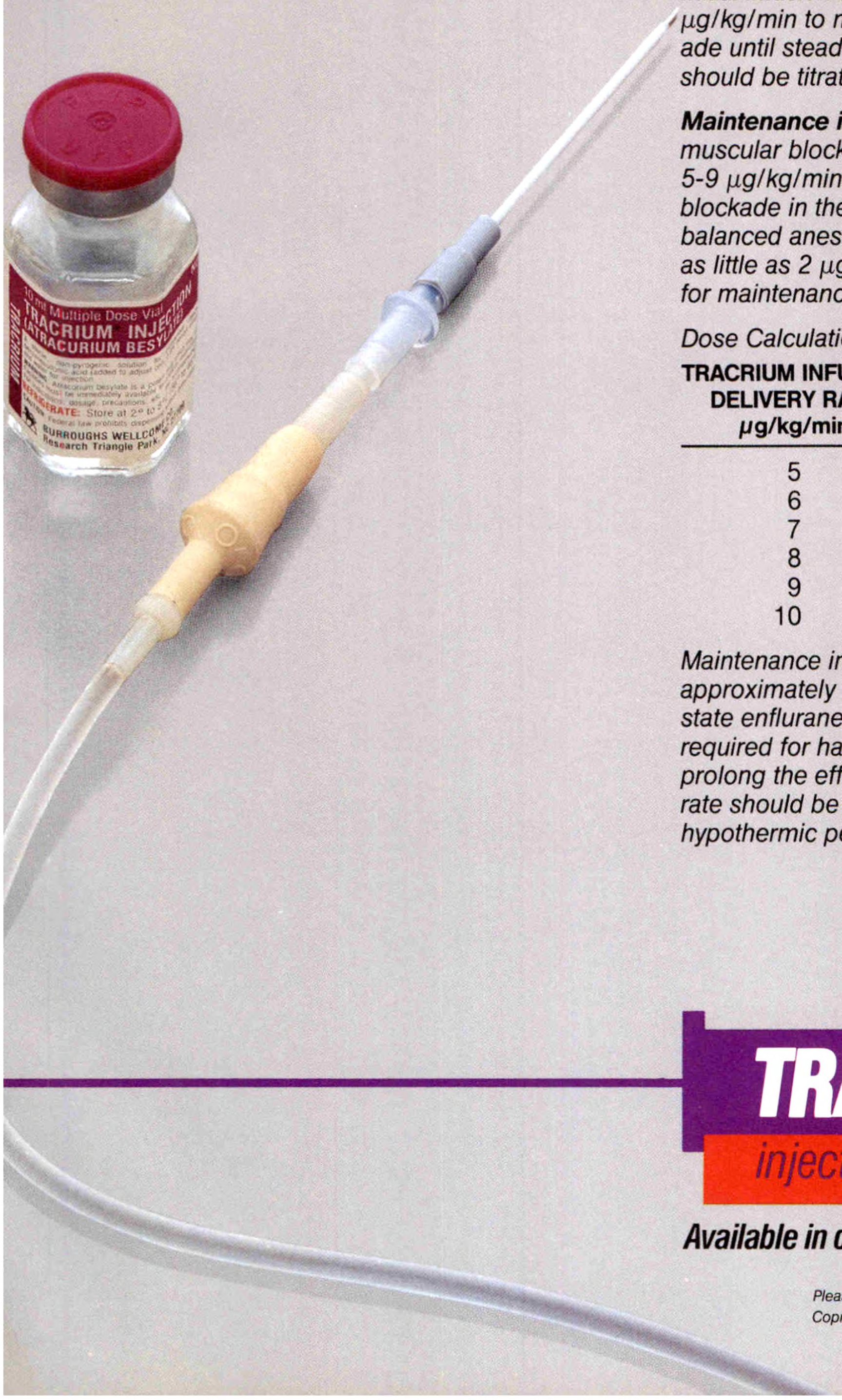
Initial infusion dose: *Infuse TRACRIUM® at a rate of 9-10 μg/kg/min to maintain 89-99% neuromuscular blockade until steady-state relaxation is achieved. Dosage should be titrated to the individual patient's needs.*

Maintenance infusion dose: *Once steady-state neuromuscular blockade is achieved, an infusion rate of 5-9 μg/kg/min is adequate to maintain continuous blockade in the 89-99% range for most patients under balanced anesthesia. Occasional patients may require as little as 2 μg/kg/min, or as much as 15 μg/kg/min for maintenance.*

Dose Calculations:

TRACRIUM INFUSION DELIVERY RATE μg/kg/min	INFUSION DELIVERY RATE 0.5 mg/mL SOLUTION mL/kg/min	mL/kg/hr
5	0.010	0.60
6	0.012	0.72
7	0.014	0.84
8	0.016	0.96
9	0.018	1.08
10	0.020	1.20

Maintenance infusion rates should be reduced by approximately one-third in the presence of steady-state enflurane or isoflurane; smaller reductions are required for halothane. Hypothermia (25°C-28°C) can prolong the effect of surgical relaxation, so infusion rate should be reduced by about one-half during the hypothermic period.



TRACRIUM®

injection (atracurium besylate)

Available in cost-effective multi-dose vials

Please see brief summary of prescribing information on the following page.

TRACRIUM® INJECTION
(atracurium besylate)

Brief Summary
This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

PRECAUTIONS:
General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether the drug is excreted in human milk.

Pediatric Use: Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS:
Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%.

Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients with 0% change in heart rate. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate.

Observed in Clinical Practice: Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequent reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

DOSAGE AND ADMINISTRATION: Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Bolus Doses for Intubation and Maintenance of Neuromuscular Blockade:
Adults: A Tracrium dose of 0.4 to 0.5 mg/kg, given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically required neuromuscular blockade generally lasts 20 to 35 minutes under balanced anesthesia. Under balanced anesthesia, recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg, to adjust for the potentiating effects of these anesthetic agents. With halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria.

Children and Infants: No Tracrium dosage adjustments are required for pediatric patients two years of age or older. A Tracrium dose of 0.3 to 0.4 mg/kg is recommended as the initial dose for infants (1 month to 2 years of age) under halothane anesthesia. Maintenance doses may be required with slightly greater frequency in infants and children than in adults.

Special Considerations: An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for adults, children, or infants with significant cardiovascular disease and for adults, children, or infants with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated. There has been no clinical experience with Tracrium in these patients, and no specific dosage adjustments can be recommended. No Tracrium dosage adjustments are required for patients with renal disease.

Use by Infusion: After administration of a recommended initial bolus dose of Tracrium (0.3 to 0.5 mg/kg), a diluted solution of Tracrium can be administered by continuous infusion to adults and children aged 2 or more years for maintenance of neuromuscular blockade during extended surgical procedures. Infusion of Tracrium should be individualized for each patient. The rate of administration should be adjusted according to the patient's response as determined by peripheral nerve stimulation.

Infusion of Tracrium should be initiated only after early evidence of spontaneous recovery from the bolus dose. An initial infusion rate of 9 to 10 μg/kg/min may be required to rapidly counteract the spontaneous recovery of neuromuscular function. Thereafter, a rate of 5 to 9 μg/kg/min should be adequate to maintain continuous neuromuscular blockade in the range of 89 to 99% in most pediatric and adult patients under balanced anesthesia.

The neuromuscular blocking effect of Tracrium administered by infusion is potentiated by enflurane or isoflurane and, to a lesser extent, by halothane. Reduction in the infusion rate of Tracrium should, therefore, be considered for patients receiving inhalation anesthesia. The rate of Tracrium infusion should be reduced by approximately one-third in the presence of steady-state enflurane or isoflurane anesthesia; smaller reductions should be considered in the presence of halothane. In patients undergoing cardiopulmonary bypass with induced hypothermia, the rate of infusion of Tracrium required to maintain adequate surgical relaxation during hypothermia (25° to 28°C) has been shown to be approximately half the rate required during normothermia.

Spontaneous recovery from neuromuscular blockade following discontinuation of Tracrium infusion may be expected to proceed at a rate comparable to that following administration of a single bolus dose.

Tracrium infusion solutions may be prepared by admixing Tracrium Injection with an appropriate diluent such as 5% Dextrose Injection USP, 0.9% Sodium Chloride Injection USP, or 5% Dextrose and 0.9% Sodium Chloride Injection USP. Infusion solutions should be used within 24 hours of preparation. Spontaneous degradation of Tracrium has been demonstrated to occur more rapidly in lactated Ringer's solution than in 0.9% sodium chloride solution. Therefore, it is recommended that Lactated Ringer's Injection USP not be used as a diluent in preparing solutions of Tracrium for infusion.

The amount of infusion solution required per minute will depend upon the concentration of Tracrium in the infusion solution and the dose of Tracrium desired (see table).

Tracrium (atracurium besylate)—Rates of Infusion for Concentrations of 0.2 and 0.5 mg/ml

Drug Delivery Rate (μg/kg/min)	Infusion Delivery Rate (ml/kg/min)	
	0.2 mg/ml*	0.5 mg/ml**
5	0.025	0.010
6	0.030	0.012
7	0.035	0.014
8	0.040	0.016
9	0.045	0.018
10	0.050	0.020

*2 ml of 1% (10 mg/ml) Tracrium Injection added to 98 ml of diluent
**5 ml of 1% (10 mg/ml) Tracrium Injection added to 95 ml of diluent

U.S. Patent No. 4179507

Wellcome
Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

TRACRIUM®
injection (atracurium besylate)

85TRA16

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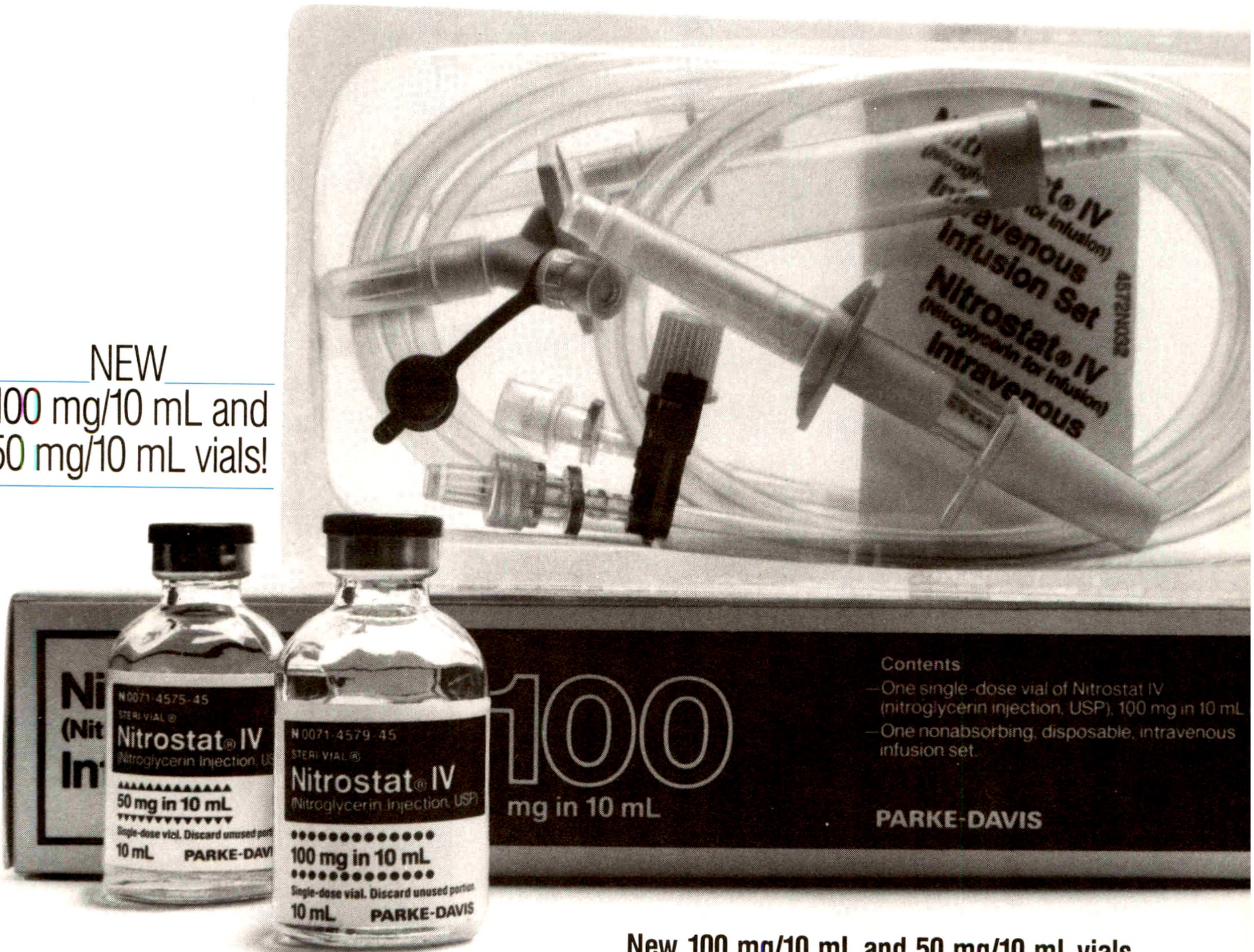
100 mg/10 mL and
50 mg/10 mL vials!



THE NITROSTAT® IV SYSTEM NOW OFFERS:

New 100 mg/10 mL and 50 mg/10 mL vials
for greater economy and convenience.

Three NITROSTAT® Strengths—
100 mg/10 mL, 50 mg/10 mL, and 8 mg/10 mL for dosage flexibility.

New improved IV infusion set
for compatibility with virtually all IV containers, including McGaw LVPs, Travenol, Abbott, and Cutter—as well as peristaltic and volumetric pumps.

NITROSTAT® IV
(nitroglycerin injection, USP)

NO OTHER IV SYSTEM COMES CLOSE

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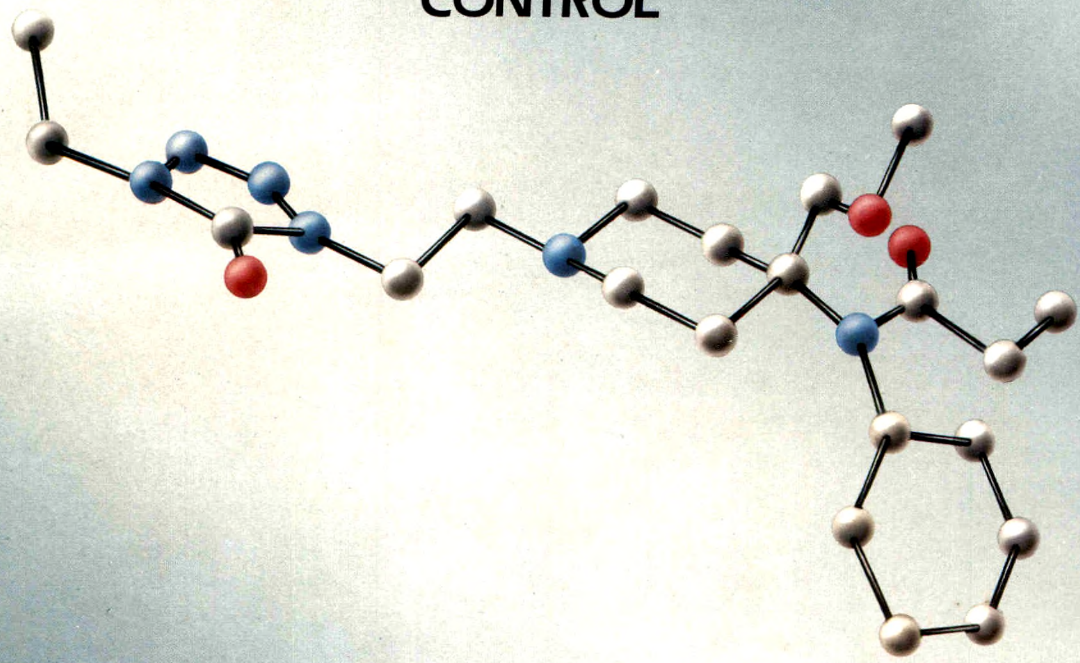
INTRODUCING

AN OPTIMAL OPIOID ANESTHETIC FOR MOMENT-TO-MOMENT CONTROL

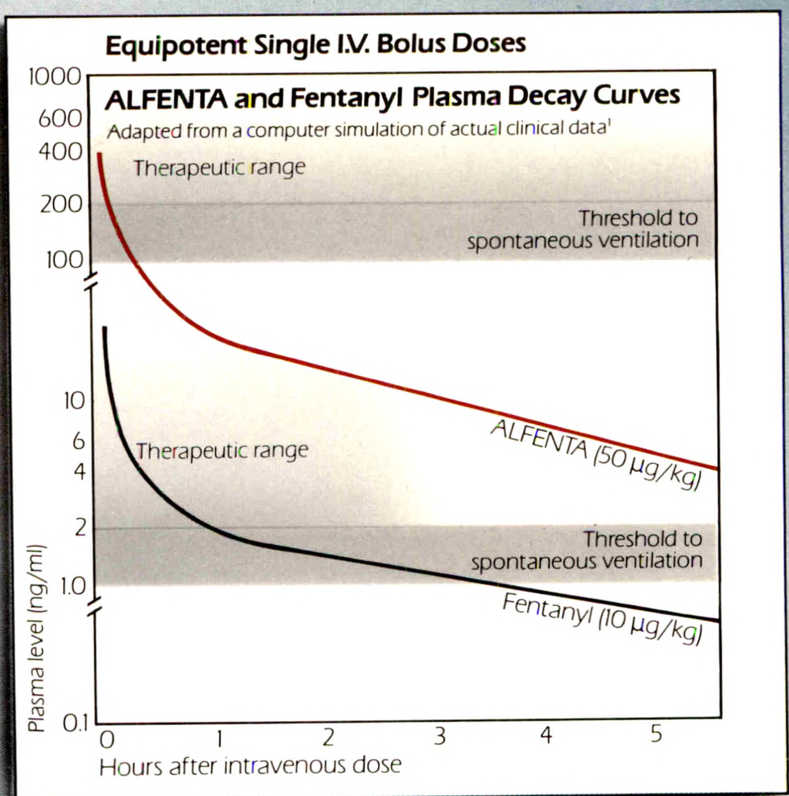


Now Available

RAPID-ACTING

Alfenta®
(alfentanil HCl) Injection CII

PROVIDES RAPID ONSET, SHORT ANALGESIC DURATION AND PROMPT RECOVERY FOR MOMENT-TO-MOMENT CONTROL IN SHORT SURGICAL PROCEDURES



Repeated or continuous administration of ALFENTA produces increasing plasma concentrations and an accumulation of the drug.

RAPID ONSET

for prompt control of hemodynamic response to surgical stimulation*

*As with other opioids, hypotension and bradycardia have been reported.

ALFENTA 1.1 minute vs. fentanyl 6.4 minutes

Onset of opioid-induced sedation as measured by maximal electroencephalographic (EEG) changes following peak plasma levels, in a clinical study comparing ALFENTA infusion 1500 µg/min and fentanyl infusion 150 µg/min.[2] ALFENTA crosses the blood brain barrier faster because at body pH, 90% is unionized while 90% of fentanyl is ionized.

SHORT DURATION OF ANALGESIC ACTION

permits titrating to patient response

The smaller volume of distribution seen with ALFENTA results in higher plasma concentrations, making more of the drug available to the liver for elimination. This results in a significantly shorter terminal elimination half-life. High intrasubject and intersubject variability in the pharmacokinetic disposition of ALFENTA has been reported.

*Patients with compromised liver function and those over 65 years of age have been found to have reduced plasma clearance and extended terminal elimination for ALFENTA, which may produce more prolonged postoperative recovery.

Comparative Pharmacokinetics in Man
(mean values following single bolus injections)

	ALFENTA[3] (N=11)	Fentanyl[4] (N=7)
Distribution ($t_{1/2}\pi$, min)	1.2	1.65
Redistribution ($t_{1/2}\alpha$, min)	11.6	13.4
Elimination ($t_{1/2}\beta$, min)	94.0	219.0
Volume of Distribution (Vd, L/kg)	0.86	4.0
Plasma Clearance* (Cl, ml/kg/min)	6.4	12.6
Protein Binding[5]	92.1[5]	84.4[5]

PROMPT RECOVERY*

In short-stay (major, minor gynecologic) procedures

Five studies[6] of patients given a mean total dose of 9.3–62.2 µg/kg of ALFENTA over 10 to 60 minutes (mean duration) reveal the following:

Number of Patients	Time to Response† to Verbal Commands	Time† to Establish Alertness
167	**2 min** (0 to 44)	**4 min** (1 to 178)

*Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained.
†Median time measured from discontinuance of nitrous oxide.

In longer (gynecologic, general) procedures using the infusion techniques: rapid return toward optimal function

Three studies[7] of patients given a mean loading dose of 45–71 µg/kg of ALFENTA, a mean infusion rate of 1.0–2.2 µg/kg/min with a mean duration of anesthesia 1.8 to 2.9 hours, reveal the following:

Number of Patients	Time† to Awake	Time† to Establish Alertness
71	**3 min** (−5 to 59)	**13 min** (0 to 64)

Please see full Prescribing Information and references at the end of this advertisement.

RAPID-ACTING

Alfenta®
(alfentanil HCl) Injection CII

OFFERS A PHARMACOKINETIC PROFILE THAT PERMITS FLEXIBILITY OF DOSING TECHNIQUE

▲ **BOLUS/INCREMENTAL ADMINISTRATION**
for short procedures

▲ **CONTINUOUS INFUSION**
for general procedures

Each ampoule contains alfentanil HCl for intravenous use, **500 µg/ml** as base.

The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery. Skeletal muscle rigidity is related to the dose and speed of administration of ALFENTA. Dosage should be individualized in each case.

Please see full Prescribing Information and references at the end of this advertisement.

ADULT DOSAGE GUIDE

BOLUS/INCREMENTAL ADMINISTRATIO

For short procedures in spontaneously breathing patients:

An initial bolus loading dose of 8 to 20 µg/kg administered before barbiturate provides analgesic protection against hemodynamic response to surgical stress with rapid recovery. In very short, relatively unstressful procedures, additional doses are often unnecessary.

For procedures lasting 30 to 60 minutes:

An initial bolus loading dose of 20 to 50 µg/kg ALFENTA, administered before thiopental, provides an analgesic level sufficient to reduce the hemodynamic response to laryngoscopy ar intubation. Additional small increments, given a needed, permit titrating to patient response.

CONTINUOUS INFUSION

For procedures lasting more than 45 minutes:

A preintubation loading dose of 50 to 75 µg/k administered over 30 to 90 seconds before thiopental, provides an analgesic level sufficient to attenuate the hemodynamic response to intubation and incision.

An average infusion rate of 1 to 1.5 µg/kg/min has been shown to provide adequate analges reduce sympathetic response to surgical stress, and provide rapid recovery with some postoperative analgesia. Changes in vital signs may generally be controlled by increasing the infusion rate and/or administration of a bolus dose of ALFENTA 7 µg/kg.

ɔrox. Duration \nesthesia	Initial Dose	Maintenance Dose	Total Dose
30 MIN ENTA administered ncremental injection, ı N_2O/O_2 ent spontaneously ıthing, ıted ventilation en required	**8-20 µg/kg** over a one- to two-min period (based on expected duration)	**3-5 µg/kg given incrementally** or **0.5-1 µg/kg/min by continuous infusion** ▲ Titrate dose to patient's respiratory response ▲ In clinical studies, maintenance doses were seldom required in cases with a duration of anesthesia of about 10 min	**8-40 µg/kg** ▲ In clinical studies, a mean total dose of approximately 30 µg/kg was required for cases of approximately 30-min duration
)-60 MIN ENTA administered ncremental injection, N_2O/O_2 ıted or controlled ilation required	**20-50 µg/kg** (based on expected duration)	**5-15 µg/kg** ▲ Clinical studies have indicated that a bolus dose of approximately 7 µg/kg may be administered to control increases in blood pressure or heart rate ▲ When responses were not controlled or recurred in these studies, up to two additional bolus doses of approximately 7 µg/kg were given over five min	**Up to 75 µg/kg**
15 MIN ENTA administered ɔntinuous infusion, N_2O/O_2 ted or controlled lation required	**50-75 µg/kg**	**0.5-3.0 µg/kg/min by continuous infusion** ▲ Changes in vital signs that indicate a response to surgical stress or lightening of anesthesia may be controlled by increasing the infusion rate up to a maximum of 4 µg/kg/min and/or administration of bolus doses of 7 µg/kg. If changes are not controlled after three bolus doses given over a five min period, a barbiturate, vasodilator, and/or inhalation agent should be used ▲ In absence of signs of lightening of anesthesia, infusion rates should always be adjusted downward until there is some response to surgical stimulation ▲ Infusion should be discontinued at least 10 to 15 min prior to the end of surgery ▲ An average ALFENTA infusion rate of 1 to 1.5 µg/kg/min has been shown to maintain hemodynamic stability, dampen sympathetic response to surgical stress and to provide rapid recovery with some postoperative analgesia ▲ Within the last 15 min of surgery, administration of approximately 7 µg/kg bolus doses of ALFENTA or a potent inhalation agent should be administered rather than increasing infusion rate in response to signs of lightening anesthesia	Dependent on duration of procedure

Alfenta®

(alfentanil HCl) Injection CII

CAUTION: Federal Law Prohibits Dispensing Without Prescription

DESCRIPTION

ALFENTA (alfentanil hydrochloride) Injection is an opioid analgesic chemically designated as N-[1-[2-(4-ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl)ethyl]-4-(methoxymethyl)-4-piperidinyl]-N-phenylpropanamide monohydrochloride (1:1) with a molecular weight of 452.98. ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 μg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.

CLINICAL PHARMACOLOGY

ALFENTA (alfentanil hydrochloride) is an opioid analgesic with a rapid onset of action.

At doses of 8-40 μg/kg for surgical procedures lasting up to 30 minutes, ALFENTA provides analgesic protection against hemodynamic responses to surgical stress with recovery times generally comparable to those seen with equipotent fentanyl dosages. For longer procedures, doses of up to 75 μg/kg attenuate hemodynamic responses to laryngoscopy, intubation and incision, with recovery time comparable to fentanyl. At doses of 50-75 μg/kg followed by a continuous infusion of 0.5-3.0 μg/kg/min, ALFENTA attenuates the catecholamine response with more rapid recovery and reduced need for postoperative analgesics as compared to patients administered enflurane. High intrasubject and intersubject variability in the pharmacokinetic disposition of ALFENTA has been reported.

The pharmacokinetics of ALFENTA as determined in 11 patients given single bolus injections of 50 or 125 μg/kg, can be described as a three-compartment model; distribution half-life ranged from 0.4-3.1 minutes; redistribution half-life ranged from 4.6-21.6 minutes; and terminal elimination half-life ranged from 64.1-129.3 minutes (as compared to a terminal elimination half-life of approximately 219 minutes for fentanyl and approximately 164 minutes for sufentanil). Linear kinetics have been described only with plasma concentrations up to 1000 ng/ml. Repeated or continuous administration of ALFENTA produces increasing plasma concentration and an accumulation of the drug, particularly in patients with reduced plasma clearance. The liver is the major site of biotransformation.

ALFENTA has an apparent volume of distribution of 0.6-1.0 L/kg, which is approximately one-fourth that of fentanyl, with a plasma clearance range of 1.7-17.6 ml/kg/min as compared to approximately 12.6 ml/kg/min for fentanyl.

Approximately 81% of the administered dose is excreted within 24 hours and only 0.2% of the dose is eliminated as unchanged drug; urinary excretion is the major route of elimination of metabolites. Plasma protein binding of ALFENTA is approximately 92%.

In one study involving 15 patients administered ALFENTA with nitrous oxide/oxygen, a narrow range of plasma ALFENTA concentrations, approximately 310-340 ng/ml, was shown to provide adequate anesthesia for intra-abdominal surgery, while lower concentrations, approximately 190 ng/ml, blocked responses to skin closure. Plasma concentrations between 100-200 ng/ml provided adequate anesthesia for superficial surgery.

ALFENTA has an immediate onset of action. At dosages of approximately 105 μg/kg, ALFENTA produces hypnosis as determined by EEG patterns; an anesthetic ED_{90} of 182 μg/kg for ALFENTA in unpremedicated patients has been determined, based upon the ability to block response to placement of a nasopharyngeal airway. Based on clinical trials, induction dosage requirements range from 130-245 μg/kg. For procedures lasting 30-60 minutes, loading dosages of up to 50 μg/kg produce the hemodynamic responses to endotracheal intubation and skin incision comparable to those from fentanyl. A pre-intubation loading dose of 50-75 μg/kg prior to a continuous infusion attenuates the response to laryngoscopy, intubation and incision. Subsequent administration of ALFENTA infusion administered at a rate of 0.5-3.0 μg/kg/min with nitrous oxide/oxygen attenuates sympathetic responses to surgical stress with more rapid recovery than enflurane.

Requirements for volatile inhalation anesthetics were reduced by thirty to fifty percent during the first 60 minutes of maintenance in patients administered anesthetic doses (above 130 μg/kg) of ALFENTA as compared to patients given doses of 4-5 mg/kg thiopental for anesthetic induction. At anesthetic induction dosages, ALFENTA provides a deep level of anesthesia during the first hour of anesthetic maintenance and provides attenuation of the hemodynamic response during intubation and incision.

Following an anesthetic induction dose of ALFENTA, requirements for ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance.

Patients with compromised liver function and those over 65 years of age have been found to have reduced plasma clearance and extended terminal elimination for ALFENTA, which may prolong postoperative recovery.

Bradycardia may be seen in patients administered ALFENTA. The incidence and degree of bradycardia may be more pronounced when ALFENTA is administered in conjunction with non-vagolytic neuromuscular blocking agents or in the absence of anticholinergic agents such as atropine.

Administration of intravenous diazepam immediately prior to or following high doses of ALFENTA has been shown to produce decreases in blood pressure that may be secondary to vasodilation; recovery may also be prolonged.

Patients administered doses up to 200 μg/kg of ALFENTA have shown no significant increase in histamine levels and no clinical evidence of histamine release.

Skeletal muscle rigidity is related to the dose and speed of administration of ALFENTA. Muscular rigidity will occur with an immediate onset following anesthetic induction dosages. Preventative measures (see WARNINGS) may reduce the rate and severity.

The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Although higher doses may produce apnea and a longer duration of respiratory depression, apnea may also occur at low doses.

INDICATIONS AND USAGE

ALFENTA (alfentanil hydrochloride) is indicated:

as an analgesic adjunct given in incremental doses in the maintenance of anesthesia with barbiturate/nitrous oxide/oxygen.

as an analgesic administered by continuous infusion with nitrous oxide/oxygen in the maintenance of general anesthesia.

as a primary anesthetic agent for the induction of anesthesia in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required.

SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF ALFENTA.

CONTRAINDICATIONS

ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS.

AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE.

BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY.

ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 μg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 μg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to ¼ of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 μg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 μg/kg).

The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS

DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.

General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight.

In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients.

In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged.

Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction.

Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery.

Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods.

The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent.

Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance.

Administration of ALFENTA infusion should be discontinued at least 10-15 minutes prior to the end of surgery.

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.

Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction.

Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.

Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits.

There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.

Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 μg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.

Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.

ADVERSE REACTIONS

The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported.

The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

	ALFENTA (N=785) %	Fentanyl (N=243) %	Thiopental Sodium (N=66) %	Enflurane (N=55) %	Halothane (N=18) %	Saline Placebo* (N=18) %
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were:

Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching.

Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.

DRUG ABUSE AND DEPENDENCE

ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE

Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD_{50} of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression.

The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

DOSAGE AND ADMINISTRATION

The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

See Dosage Chart for the use of ALFENTA: 1) by incremental injection as an analgesic adjunct to anesthesia with barbiturate / nitrous oxide / oxygen for short surgical procedures (expected duration of less than one hour); 2) by continuous infusion as a maintenance analgesic with nitrous oxide / oxygen for general surgical procedures; and 3) by intravenous injection in anesthetic doses for the induction of anesthesia for general surgical procedures with a minimum expected duration of 45 minutes.

Usage in Children: Clinical data to support the use of ALFENTA in patients under 12 years of age are not presently available. Therefore, such use is not recommended.

Premedication: The selection of preanesthetic medications should be based upon the needs of the individual patient.

Neuromuscular Blocking Agents: The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS sections).

In patients administered anesthetic (induction) dosages of ALFENTA, it is essential that qualified personnel and adequate facilities are available for the management of intraoperative and postoperative respiratory depression.

Also see WARNINGS and PRECAUTIONS sections.

For purposes of administering small volumes of ALFENTA accurately, the use of a tuberculin syringe or equivalent is recommended.

The physical and chemical compatibility of ALFENTA have been demonstrated in solution with normal saline, 5% dextrose in normal saline, 5% dextrose in water and Lactated Ringers. Clinical studies of ALFENTA infusion have been conducted with ALFENTA diluted to a concentration range of 25 μg/ml to 80 μg/ml.

As an example of the preparation of ALFENTA for infusion, 20 ml of ALFENTA added to 230 ml of diluent provides a 40 μg/ml solution of ALFENTA.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

DOSAGE RANGE CHART

Indication	Incremental Injection	Incremental Injection	Continuous Infusion*	Anesthetic Induction
Approximate Duration of Anesthesia	≤ 30 mins	30-60 mins	> 45 mins	> 45 mins
Induction Period (Initial Dose)	8-20 μg/kg	20-50 μg/kg	50-75 μg/kg	130-245 μg/kg
Maintenance Period (Increments/ Infusion)	3-5 μg/kg or 0.5-1 μg/kg/min	5-15 μg/kg	0.5-3.0 μg/kg/min Average Infusion Rate 1-1.5 μg/kg/min	0.5 to 1.5 μg/kg/min or general anesthetic
Total Dose	8-40 μg/kg	up to 75 μg/kg	dependent on duration of procedure	dependent on duration of procedure
Effects	Spontaneously breathing or assisted ventilation when required.	Assisted or controlled ventilation required. Attenuation of response to laryngoscopy and intubation.	Assisted or controlled ventilation required. Some attenuation of response to intubation and incision, with intraoperative stability.	Assisted or controlled ventilation required. Administer slowly (over three minutes). Concentration of inhalation agents reduced by 30-50% for initial hour.

INFUSION DOSAGE

***Continuous Infusion:** 0.5-3.0 μg/kg/min administered with nitrous oxide / oxygen in patients undergoing general surgery. Following an anesthetic induction dose of ALFENTA, infusion rate requirements are reduced by 30-50% for the first hour of maintenance.

Changes in vital signs that indicate a response to surgical stress or lightening of anesthesia may be controlled by increasing the rate up to a maximum of 4.0 μg/kg/min and/or administration of bolus doses of 7 μg/kg. If changes are not controlled after three bolus doses given over a five minute period, a barbiturate, vasodilator, and/or inhalation agent should be used. Infusion rates should always be adjusted downward in the absence of these signs until there is some response to surgical stimulation.

Rather than an increase in infusion rate, 7 μg/kg bolus doses of ALFENTA or a potent inhalation agent should be administered in response to signs of lightening of anesthesia within the last 15 minutes of surgery. Administration of ALFENTA infusion should be discontinued at least 10-15 minutes prior to the end of surgery.

HOW SUPPLIED

Each ml of ALFENTA (alfentanil hydrochloride) Injection for intravenous use contains alfentanil hydrochloride equivalent to 500 μg of alfentanil base. ALFENTA Injection is available as:

NDC 50458-060-02, 2 ml ampoules in packages of 10
NDC 50458-060-05, 5 ml ampoules in packages of 10
NDC 50458-060-10, 10 ml ampoules in packages of 5
NDC 50458-060-20, 20 ml ampoules in packages of 5

Protect from light. Store at room temperature 15°-30°C (59°-86°F).
U.S. Patent No. 4,167,574   March 1987   49-7619901-M

Manufactured by Taylor Pharmacal Co. for

JANSSEN
PHARMACEUTICA
Piscataway, NJ 08854

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Anesthesia Foundation Book Award

The Anesthesia Foundation announces the fifth award of five thousand dollars for a book judged to be the best written in the field of anesthesiology and submitted before September 15, 1988. The award will be given only to an anesthesiologist working and living in North America.

The award will be given only for a first edition. A book may not have more than two authors, and the senior author must be an anesthesiologist. Books that are part of a series, where each chapter has a different author, will not be eligible. Symposia and reports of meetings are also ineligible. Textbooks will be considered if there are not more than two authors.

The award will be based on timeliness, timelessness, originality, teaching value, sophistication, literary style, illustrations, scientific excellence, succinctness, impact, permanent value, format, and references.

If, in the opinion of the judges, no book merits the award, no award will be made.

Books may be submitted by the author or the book publisher. Books must be received no later than September 15, 1988. Books may have a copyright date of 1987 or 1988, but if they are received after September 15, 1988, they will be considered for the following award, provided a sixth book award is offered.

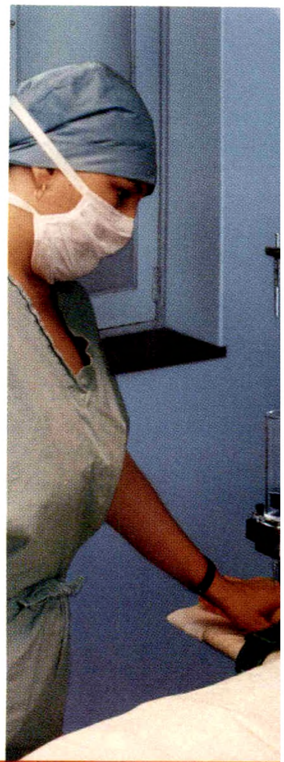
One copy should be sent to each of the three judges:

Nicholas M. Greene, MD, Professor
Department of Anesthesiology
Yale University School of Medicine
333 Cedar Street
New Haven, Connecticut 06510

Joseph F. Artusio Jr, MD
Secretary, The Anesthesia Foundation
525 East 68th Street
New York, New York 10021
Attention: Department of Anesthesiology

Leroy D. Vandam, MD
Department of Anesthesia
Brigham and Women's Hospital
75 Francis Street
Boston, Massachusetts 02115

For outpatient anesthesia



Rapid

Well-suited to the rapid turnover of outpatient cases, the low solubility of isoflurane in blood and tissue (only that of nitrous oxide is lower) enables you to quickly adjust the level of anesthesia to patient and surgical requirements.

Following anesthesia, a rapid washout and prompt recovery provide for your early patient assessment. Patient alertness and cooperation can facilitate handling in the outpatient setting.

Complete

Without *any* other agent or premedicant, isoflurane provides *every* action required for a complete anesthetic, on a closely controlled, breath-by-breath basis: unconsciousness, surgical analgesia, amnesia, and good surgical muscle relaxation—a useful advantage for laparoscopies and orthopedic work, and one that begins when the anesthetic begins and *ends* with elimination of the anesthetic, thereby decreasing the risk of residual paralysis in the PAR.

Because isoflurane is a complete anesthetic when given alone in oxygen or room air, *nitrous oxide can be eliminated* if you choose. Isoflurane anesthetics are seldom complicated and prolonged by postoperative nausea and vomiting.

FORANE® (isoflurane, USP)

Excellent Safety Profile

Stability of heart rhythm and good cardiac output are notable features of an isoflurane anesthetic. CNS excitation does not occur at any concentration or $PaCO_2$ level. Virtually 100% of isoflurane is exhaled unchanged from the patient (only 0.17% of the isoflurane taken up is recovered as metabolites). This near absence of metabolic by-products all but assures an absence of hepatic or renal toxicity from metabolism.

Anaquest

BOC Health Care

For outpatient anesthesia

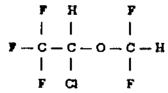
FORANE® (isoflurane, USP)

Rapid...Complete...Excellent Safety Profile

CAUTION: Federal Law Prohibits Dispensing without Prescription.

DESCRIPTION

FORANE (isoflurane, USP) a nonflammable liquid administered by vaporizing, is a general inhalation anesthetic drug. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



Some physical constants are:

Molecular weight		184.5
Boiling point at 760 mm Hg		48.5 °C (uncorr.)
Refractive index n_D^{20}		1.2990-1.3005
Specific gravity 25 °/25 °C		1.496
Vapor pressure in mm Hg**	20 °C	238
	25 °C	295
	30 °C	367
	35 °C	450

**Equation for vapor pressure calculation:

$$\log_{10}P_{vap} = A + \frac{B}{T} \quad \text{where: } A = 8.056,\ B = -1664.58,\ T = {}^\circ C + 273.16\ (\text{Kelvin})$$

Partition coefficients at 37 °C	
Water/gas	0.61
Blood/gas	1.43
Oil/gas	90.8

Partition coefficients at 25 °C - rubber and plastic	
Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinyl chloride/gas	110.0
Polyethylene/gas	~2.0
Polyurethane/gas	~1.4
Polyolefin/gas	~1.1
Butyl acetate/gas	~2.5

Purity by gas chromatography	>99.9%
Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec. and 23 °C	None
Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec. and 23 °C	Greater than useful concentration in anesthesia.

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave U.V. light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

CLINICAL PHARMACOLOGY

FORANE (isoflurane, USP) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is as follows:

Age	100% Oxygen	70% N_2O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal $PaCO_2$, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 mL of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

Pharmacokinetics: Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

INDICATIONS AND USAGE

FORANE (isoflurane, USP) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Known sensitivity to FORANE (isoflurane, USP) or to other halogenated agents.

Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS

Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

FORANE (isoflurane, USP) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

PRECAUTIONS

General: As with any potent general anesthetic, FORANE (isoflurane, USP) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

Information to Patients: Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N_2O.
See CLINICAL PHARMACOLOGY.

Carcinogenesis: Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have a possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO_2 absorption system (hot canister). PaO_2 and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

ADVERSE REACTIONS

Adverse reactions encountered in the administration of FORANE (isoflurane, USP) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting and ileus have been observed in the postoperative period. As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

OVERDOSAGE

In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION

Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane, USP) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for isoflurane;

b) vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula:

$$\%\ \text{isoflurane} = \frac{100\ P_V\ F_V}{F_T\ (P_A - P_V)}$$

where: P_A = Pressure of atmosphere
P_V = Vapor pressure of isoflurane
F_V = Flow of gas through vaporizer (mL/min)
F_T = Total gas flow (mL/min)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia may be sustained with a 1.0 to 2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5 to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

HOW SUPPLIED

FORANE (isoflurane, USP), NDC 10019-360-40, is packaged in 100 mL amber-colored bottles.

Storage: Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

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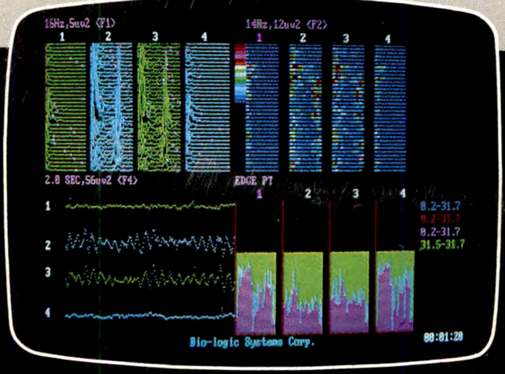

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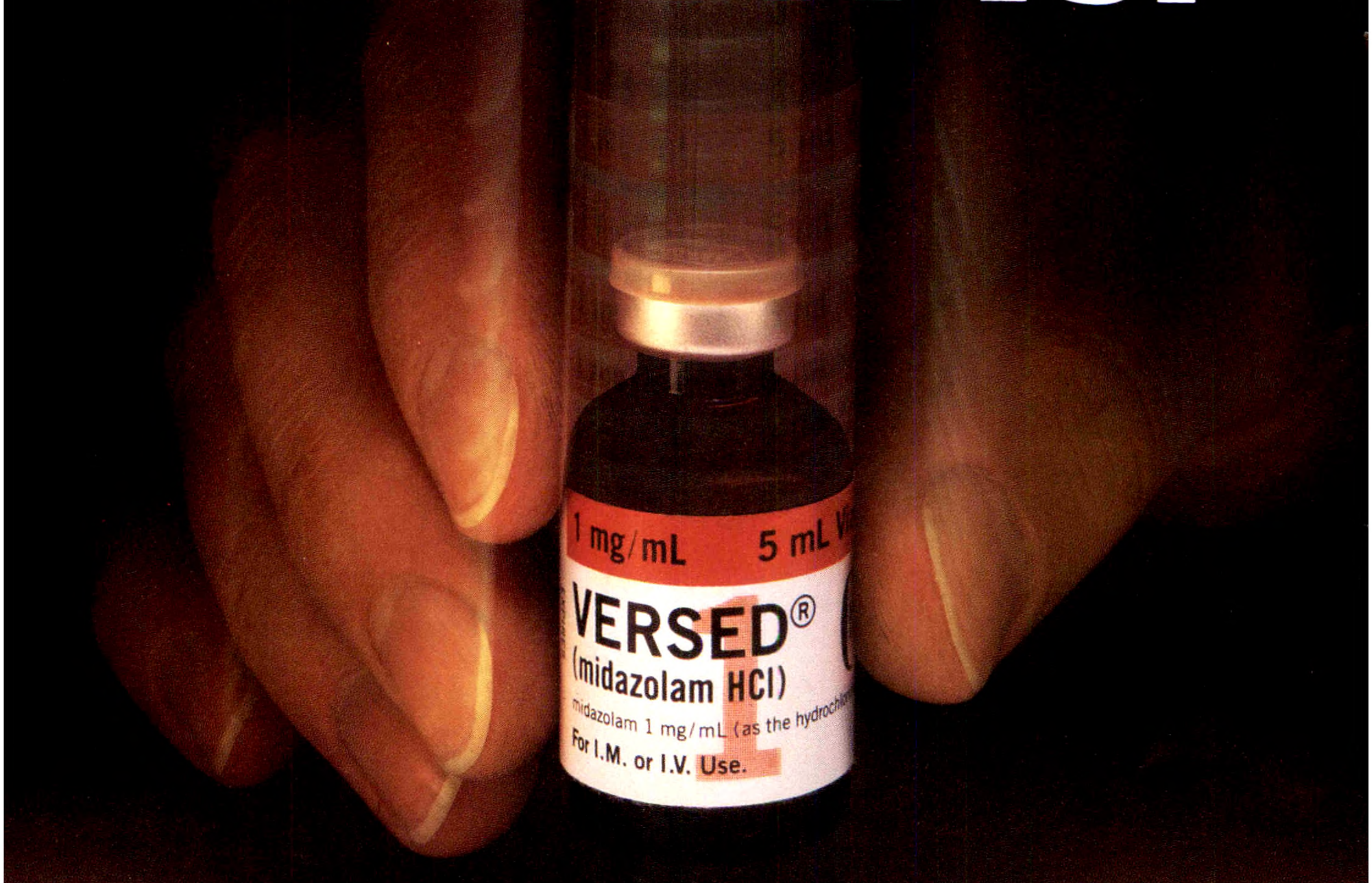

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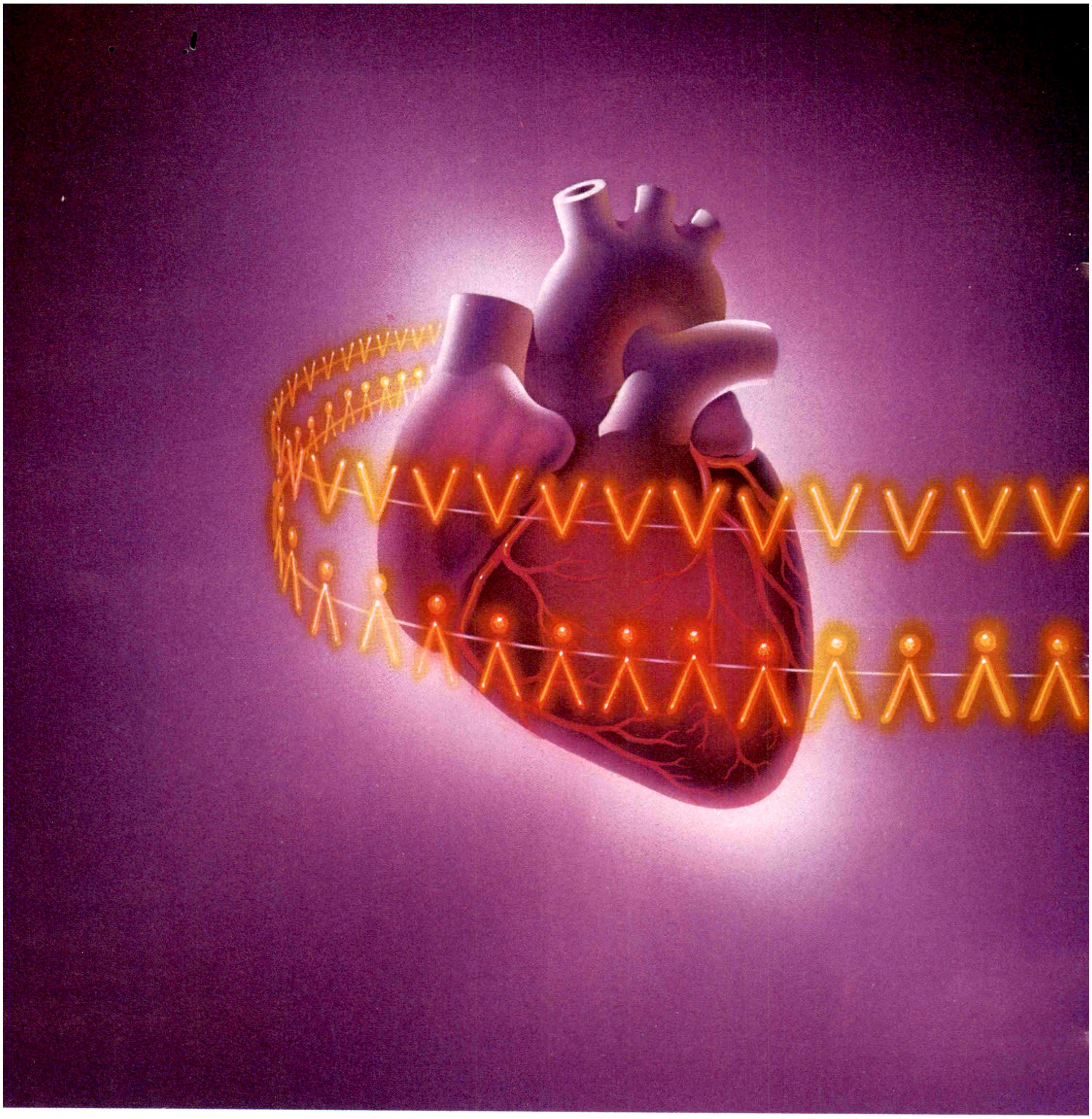

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"Development of a Program to Assess Clinical Performance of Resident Physicians in Anesthesia"

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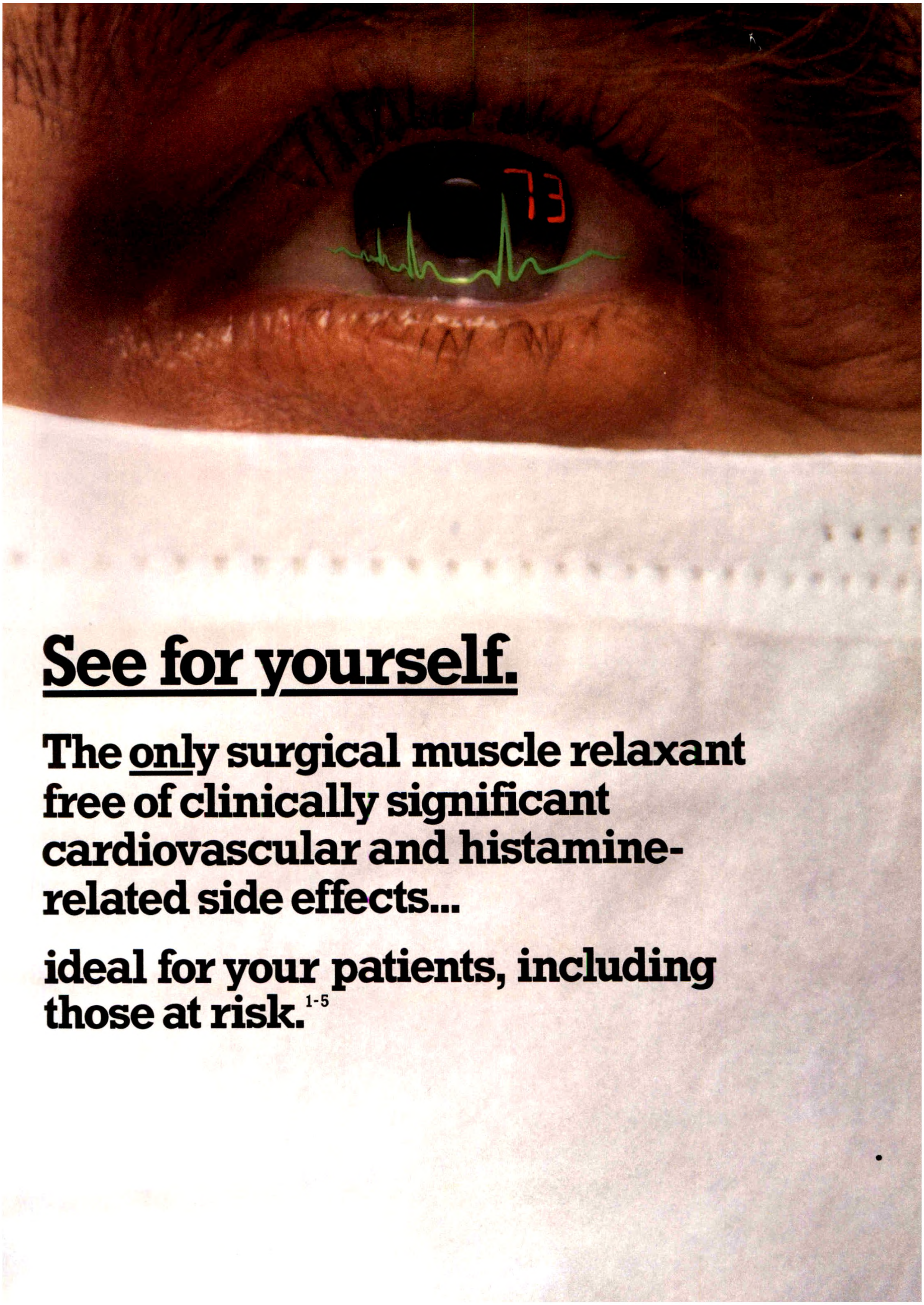
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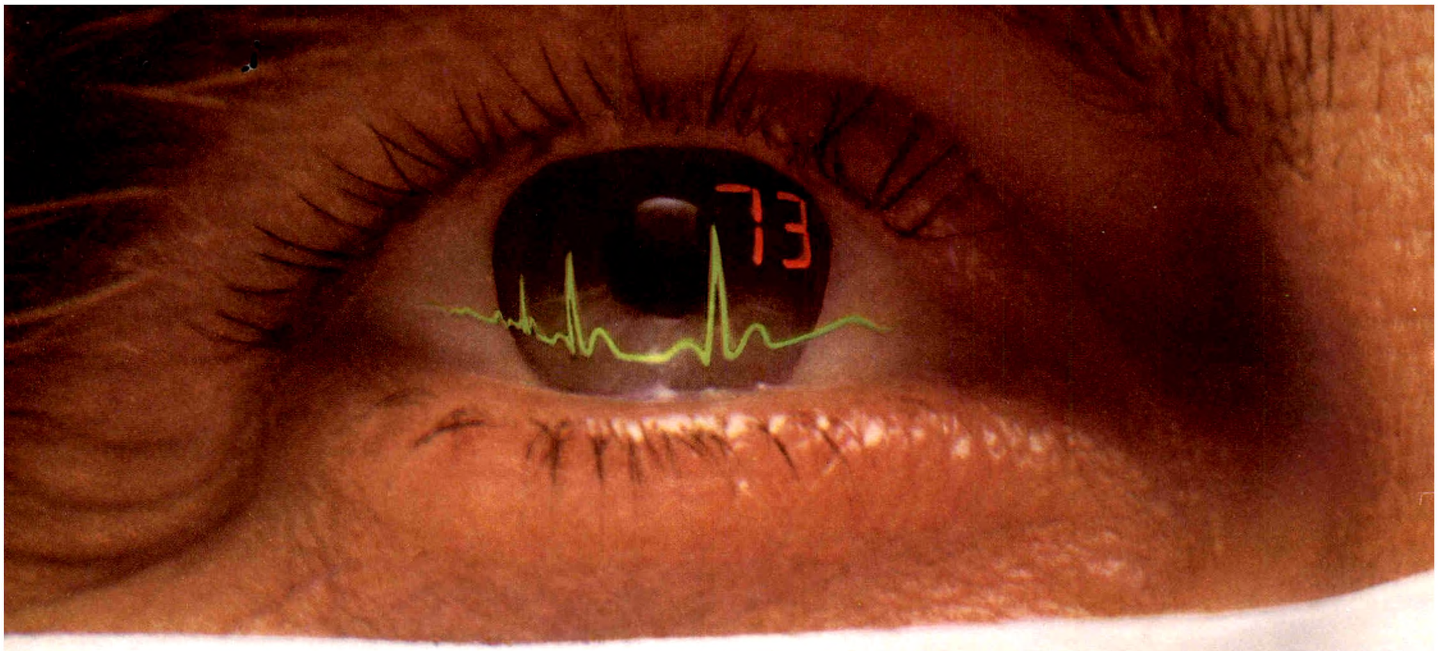

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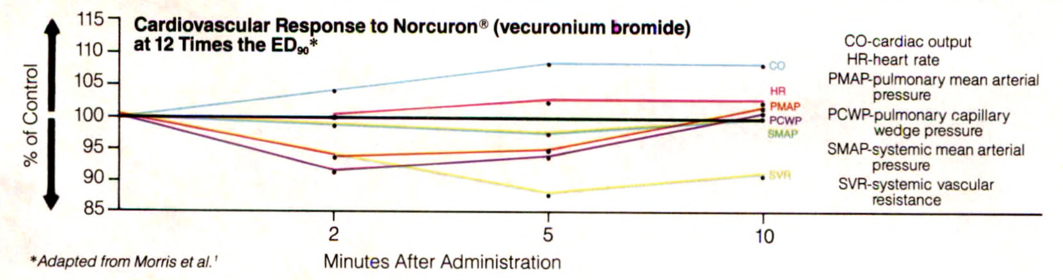

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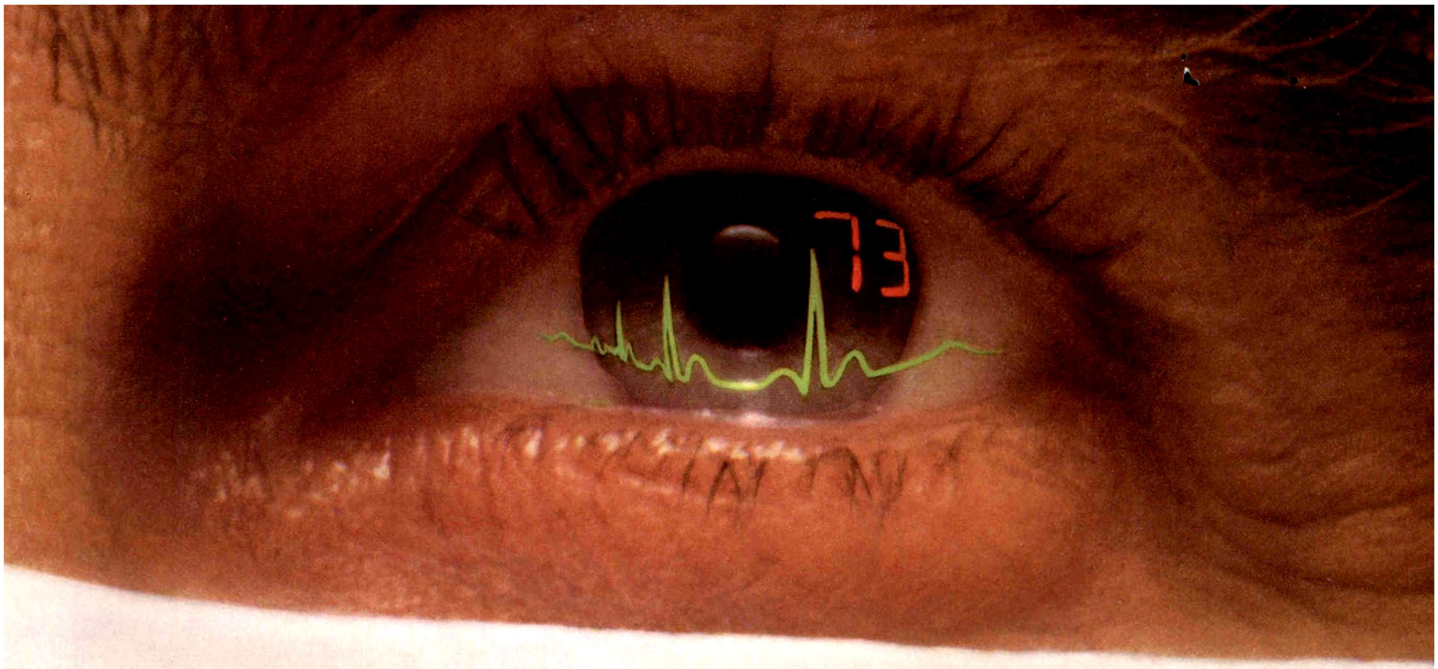
NORCURON® has not been shown to significantly affect circulating histamine, mean arterial blood pressure, and heart rate even in doses at the upper extreme of the recommended clinical range.[5]

The Effect of Nondepolarizing Muscle Relaxants*

Drug	Dose (mg/kg)	xED_{95}	Histamine	Mean Arterial Pressure	Heart Rate
			Percent of Control		
Tubocurarine	0.5	1	410	78	116
Metocurine	0.5†	2	212	79	119
Atracurium	0.6†	3	192	80	108
Vecuronium	0.1	1.7	117	100	99
Vecuronium	0.2	3.5	87	99	102

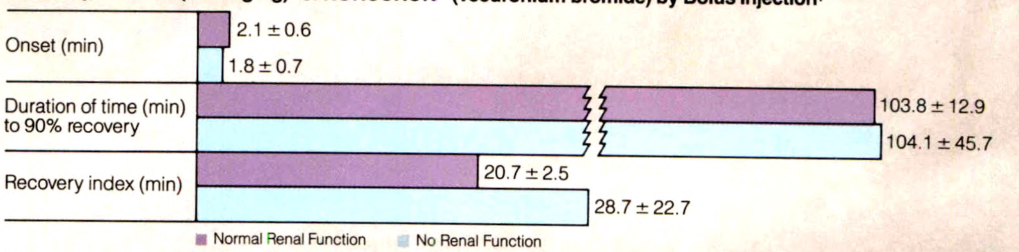
*Adapted from Basta et al.[5]
†0.1 mg/kg higher than recommended dose.



Performance unaffected by renal function.[6]

Despite administration of high doses of NORCURON®, no significant differences in onset time, duration of action, or recovery index have been noted between patients with and without renal function.[6]

Comparative Indices of Neuromuscular Blockade for Patients With and Without Renal Function Given Equal Doses (0.14 mg/kg)* of NORCURON® (vecuronium bromide) by Bolus Injection†



*Although high doses of NORCURON® were used to assess its pharmacokinetics, it is recommended that the initial dose not exceed 0.08 to 0.1 mg/kg.
†Adapted from Miller et al.[6]

The surgical muscle relaxant ideal for virtually all patients including those at risk.

Norcuron®
(vecuronium bromide) injection

See full prescribing information on following page.

References: 1. Morris RB, et al: The cardiovascular effects of vecuronium (ORG NC 45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1983; 58:438-440. **2.** Durant NN: Norcuron®—a new nondepolarizing neuromuscular blocking agent. *Semin Anesth* 1982; 1:47-56. **3.** Krieg N, Crul JF, Booij LH: Relative potency of ORG NC 45, pancuronium, alcuronium, and tubocurarine in anesthetized man. *Br J Anaesth* 1980; 52:783-787. **4.** Gallo JA, et al: Hemodynamic effects of bolus injection of vecuronium in cardiac surgical patients. *Anesthesiology* 1984; 61:A63. **5.** Basta SJ, et al: Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiology* 1983; 59:A273. **6.** Miller RD, et al: Pharmacokinetics of vecuronium in patients with kidney disease, in Agoston S, et al (eds): *Clinical Experiences with Norcuron (ORG NC 45, Vecuronium Bromide).* Amsterdam, Excerpta Medica, 1983, p 124.

Norcuron® (vecuronium bromide) injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: NORCURON® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2β, 3α, 5α, 16β, 17β)-3, 17-bis(acetyloxy)-2-(1-piperidinyl)androstan-16-yl]-1-methyl-, bromide.

Norcuron® is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

CLINICAL PHARMACOLOGY: Norcuron® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about ⅓ more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron® doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED_{90} (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® may be decreased by approximately 15% (see DOSAGE AND ADMINISTRATION section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the neuromuscular block produced by Norcuron® is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron® induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

Pharmacokinetics: At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron® varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron® (vecuronium bromide) injection has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron®; equipotent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron®. Limited data derived from patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary capillary wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease). Limited clinical experience (3 patients) with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

INDICATIONS AND USAGE: Norcuron® is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: None known.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: Renal Failure: Norcuron® is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

●**Hepatic Disease:** Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTANT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

Norcuron® has no known effect on consciousness, the pain theshold or cerebration. Administration must be accompanied by adequate anesthesia.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY). The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®; therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron® during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

OVERDOSAGE: There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve.

NO REFRIGERATION REQUIRED

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION: Norcuron® (vecuronium bromide) injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution — 5% glucose in saline
5% glucose in water — Lactated Ringer's

HOW SUPPLIED: 5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile water for injection as the diluent. Boxes of 10 (NDC#0052-0442-17).

5 ml vials (contains 10 mg of active ingredient) only. DILUENT (Sterile Water for Injection, USP) NOT SUPPLIED. Boxes of 10 (NDC#0052-0442-57).

STORAGE: PROTECT FROM LIGHT. Store at 15°-30°C (59°-86°F).

AFTER RECONSTITUTION: Solution may be stored in refrigerator or kept at room temperature not to exceed 30°C (86°F). DISCARD SOLUTION AFTER 24 HOURS. DISCARD UNUSED PORTION. SINGLE USE VIALS.

Manufactured for ORGANON INC. by BEN VENUE LABORATORIES, INC., Bedford, OH 44146 ISSUED 5/86

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ORGANON INC.
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ORG-8025

Anesthesia Foundation Book Award

The Anesthesia Foundation announces the fifth award of five thousand dollars for a book judged to be the best written in the field of anesthesiology and submitted before September 15, 1988. The award will be given only to an anesthesiologist working and living in North America.

The award will be given only for a first edition. A book may not have more than two authors, and the senior author must be an anesthesiologist. Books that are part of a series, where each chapter has a different author, will not be eligible. Symposia and reports of meetings are also ineligible. Textbooks will be considered if there are not more than two authors.

The award will be based on timeliness, timelessness, originality, teaching value, sophistication, literary style, illustrations, scientific excellence, succinctness, impact, permanent value, format, and references.

If, in the opinion of the judges, no book merits the award, no award will be made.

Books may be submitted by the author or the book publisher. Books must be received no later than September 15, 1988. Books may have a copyright date of 1987 or 1988, but if they are received after September 15, 1988, they will be considered for the following award, provided a sixth book award is offered.

One copy should be sent to each of the three judges:

Nicholas M. Greene, MD, Professor
Department of Anesthesiology
Yale University School of Medicine
333 Cedar Street
New Haven, Connecticut 06510

Joseph F. Artusio Jr, MD
Secretary, The Anesthesia Foundation
525 East 68th Street
New York, New York 10021
Attention: Department of Anesthesiology

Leroy D. Vandam, MD
Department of Anesthesia
Brigham and Women's Hospital
75 Francis Street
Boston, Massachusetts 02115

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

IARS 62nd CONGRESS

March 5–9, 1988—HOTEL INTER-CONTINENTAL—SAN DIEGO, CALIFORNIA

CALL FOR PAPERS

AUGUST 5, 1987 DEADLINE

The Program Committee for the IARS 62nd Congress cordially invites submission of abstracts for consideration as oral or poster presentations at the 1988 meeting in San Diego. The official abstract application and transmittal forms are available from the Cleveland office of the IARS:

International Anesthesia Research Society
3645 Warrensville Center Road
Cleveland, OH 44122, USA
Telephone: (216) 295-1124

Please note the absolute deadline for receipt of completed applications is August 5, 1987. Please request forms promptly—either by calling the telephone number above or returning the form below.

Noel W. Lawson, MD, Chairman
62nd Congress Program Committee

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, Ohio 44122

Please send ______ abstract submission packet(s) for the IARS 62nd Congress to:

Name: ____

Mail Address: ______________________________________

____

RAPID ONSET
for prompt control of hemodynamic response to surgical stimulation*

As with other opioids, hypotension and bradycardia have been reported.

ALFENTA 1.1 minute vs. fentanyl 6.4 minutes

Onset of opioid-induced sedation as measured by maximal electroencephalographic (EEG) changes following peak plasma levels, in a clinical study comparing ALFENTA infusion 1500 µg/min and fentanyl infusion 150 µg/min.[2] ALFENTA crosses the blood brain barrier faster because at body pH, 90% is unionized while 90% of fentanyl is ionized.

SHORT DURATION OF ANALGESIC ACTION
permits titrating to patient response

The smaller volume of distribution seen with ALFENTA results in higher plasma concentrations, making more of the drug available to the liver for elimination. This results in a significantly shorter terminal elimination half-life. High intrasubject and intersubject variability in the pharmacokinetic disposition of ALFENTA has been reported.

*Patients with compromised liver function and those over 65 years of age have been found to have reduced plasma clearance and extended terminal elimination for ALFENTA, which may produce more prolonged postoperative recovery.

Comparative Pharmacokinetics in Man
(mean values following single bolus injections)

	ALFENTA[3] (N=11)	Fentanyl[4] (N=7)
Distribution ($t\,\frac{1}{2}\pi$, min)	1.2	1.65
Redistribution ($t\,\frac{1}{2}\alpha$, min)	11.6	13.4
Elimination ($t\,\frac{1}{2}\beta$, min)	94.0	219.0
Volume of Distribution (Vd, L/kg)	0.86	4.0
Plasma Clearance* (Cl, ml/kg/min)	6.4	12.6
Protein Binding[5]	92.1[5]	84.4[5]

PROMPT RECOVERY*

In short-stay (major, minor gynecologic) procedures

Five studies[6] of patients given a mean total dose of 9.3–62.2 µg/kg of ALFENTA over 10 to 60 minutes (mean duration) reveal the following:

Number of Patients	Time to Response† to Verbal Commands	Time† to Establish Alertness
167	**2 min** (0 to 44)	**4 min** (1 to 178)

Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained.
†Median time measured from discontinuance of nitrous oxide.

In longer (gynecologic, general) procedures using the infusion techniques: rapid return toward optimal function

Three studies[7] of patients given a mean loading dose of 45–71 µg/kg of ALFENTA, a mean infusion rate of 1.0–2.2 µg/kg/min with a mean duration of anesthesia 1.8 to 2.9 hours, reveal the following:

Number of Patients	Time† to Awake	Time† to Establish Alertness
71	**3 min** (–5 to 59)	**13 min** (0 to 64)

Please see full Prescribing Information and references at the end of this advertisement.

RAPID-ACTING

Alfenta®
(alfentanil HCl) Injection CII

OFFERS A PHARMACOKINETIC PROFILE THAT PERMITS FLEXIBILITY OF DOSING TECHNIQUE

▲ **BOLUS/INCREMENTAL ADMINISTRATION**
for short procedures

▲ **CONTINUOUS INFUSION**
for general procedures

Each ampoule contains alfentanil HCl for intravenous use, **500 µg/ml** as base.

The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery. Skeletal muscle rigidity is related to the dose and speed of administration of ALFENTA. Dosage should be individualized in each case.

Please see full Prescribing Information and references at the end of this advertisement.

ADULT DOSAGE GUIDE

BOLUS/INCREMENTAL ADMINISTRATIO

For short procedures in spontaneously breathing patients:

An initial bolus loading dose of 8 to 20 µg/kg administered before barbiturate provides analgesic protection against hemodynamic response to surgical stress with rapid recovery. In very short, relatively unstressful procedures, additional doses are often unnecessary.

For procedures lasting 30 to 60 minutes:

An initial bolus loading dose of 20 to 50 µg/kg ALFENTA, administered before thiopental, provides an analgesic level sufficient to reduce the hemodynamic response to laryngoscopy a intubation. Additional small increments, given needed, permit titrating to patient response.

CONTINUOUS INFUSION

For procedures lasting more than 45 minutes:

A preintubation loading dose of 50 to 75 µg/k administered over 30 to 90 seconds before thiopental, provides an analgesic level sufficien to attenuate the hemodynamic response to intubation and incision.

An average infusion rate of 1 to 1.5 µg/kg/min has been shown to provide adequate analges reduce sympathetic response to surgical stress, and provide rapid recovery with some postoperative analgesia. Changes in vital signs may generally be controlled by increasing the infusion rate and/or administration of a bolus dose of ALFENTA 7 µg/kg.

ɔrox. Duration \nesthesia	Initial Dose	Maintenance Dose	Total Dose
ɜ0 MIN ENTA administered ıcremental injection, ı N_2O/O_2 ent spontaneously thing, ted ventilation en required	**8-20 µg/kg** over a one- to two-min period (based on expected duration)	**3-5 µg/kg given incrementally** or **0.5-1 µg/kg/min by continuous infusion** ▲ Titrate dose to patient's respiratory response ▲ In clinical studies, maintenance doses were seldom required in cases with a duration of anesthesia of about 10 min	**8-40 µg/kg** ▲ In clinical studies, a mean total dose of approximately 30 µg/kg was required for cases of approximately 30-min duration
ı-60 MIN ENTA administered ıcremental injection, N_2O/O_2 ted or controlled ilation required	**20-50 µg/kg** (based on expected duration)	**5-15 µg/kg** ▲ Clinical studies have indicated that a bolus dose of approximately 7 µg/kg may be administered to control increases in blood pressure or heart rate ▲ When responses were not controlled or recurred in these studies, up to two additional bolus doses of approximately 7 µg/kg were given over five min	**Up to 75 µg/kg**
ŀ5 MIN ENTA administered ɔntinuous infusion, N_2O/O_2 ted or controlled lation required	**50-75 µg/kg**	**0.5-3.0 µg/kg/min by continuous infusion** ▲ Changes in vital signs that indicate a response to surgical stress or lightening of anesthesia may be controlled by increasing the infusion rate up to a maximum of 4 µg/kg/min and/or administration of bolus doses of 7 µg/kg. If changes are not controlled after three bolus doses given over a five min period, a barbiturate, vasodilator, and/or inhalation agent should be used ▲ In absence of signs of lightening of anesthesia, infusion rates should always be adjusted downward until there is some response to surgical stimulation ▲ Infusion should be discontinued at least 10 to 15 min prior to the end of surgery ▲ An average ALFENTA infusion rate of 1 to 1.5 µg/kg/min has been shown to maintain hemodynamic stability, dampen sympathetic response to surgical stress and to provide rapid recovery with some postoperative analgesia ▲ Within the last 15 min of surgery, administration of approximately 7 µg/kg bolus doses of ALFENTA or a potent inhalation agent should be administered rather than increasing infusion rate in response to signs of lightening anesthesia	Dependent on duration of procedure

Alfenta®

(alfentanil HCl) Injection CII

CAUTION: Federal Law Prohibits Dispensing Without Prescription

DESCRIPTION

ALFENTA (alfentanil hydrochloride) Injection is an opioid analgesic chemically designated as N-[1-[2-(4-ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl)ethyl]-4-(methoxymethyl)-4-piperidinyl]-N-phenylpropanamide monohydrochloride (1:1) with a molecular weight of 452.98. ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 μg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.

CLINICAL PHARMACOLOGY

ALFENTA (alfentanil hydrochloride) is an opioid analgesic with a rapid onset of action.

At doses of 8-40 μg/kg for surgical procedures lasting up to 30 minutes, ALFENTA provides analgesic protection against hemodynamic responses to surgical stress with recovery times generally comparable to those seen with equipotent fentanyl dosages. For longer procedures, doses of up to 75 μg/kg attenuate hemodynamic responses to laryngoscopy, intubation and incision, with recovery time comparable to fentanyl. At doses of 50-75 μg/kg followed by a continuous infusion of 0.5-3.0 μg/kg/min, ALFENTA attenuates the catecholamine response with more rapid recovery and reduced need for postoperative analgesics as compared to patients administered enflurane. High intrasubject and intersubject variability in the pharmacokinetic disposition of ALFENTA has been reported.

The pharmacokinetics of ALFENTA as determined in 11 patients given single bolus injections of 50 or 125 μg/kg, can be described as a three-compartment model; distribution half-life ranged from 0.4-3.1 minutes; redistribution half-life ranged from 4.6-21.6 minutes; and terminal elimination half-life ranged from 64.1-129.3 minutes (as compared to a terminal elimination half-life of approximately 219 minutes for fentanyl and approximately 164 minutes for sufentanil). Linear kinetics have been described only with plasma concentrations up to 1000 ng/ml. Repeated or continuous administration of ALFENTA produces increasing plasma concentration and an accumulation of the drug, particularly in patients with reduced plasma clearance. The liver is the major site of biotransformation.

ALFENTA has an apparent volume of distribution of 0.6-1.0 L/kg, which is approximately one-fourth that of fentanyl, with a plasma clearance range of 1.7-17.6 ml/kg/min as compared to approximately 12.6 ml/kg/min for fentanyl.

Approximately 81% of the administered dose is excreted within 24 hours and only 0.2% of the dose is eliminated as unchanged drug; urinary excretion is the major route of elimination of metabolites. Plasma protein binding of ALFENTA is approximately 92%.

In one study involving 15 patients administered ALFENTA with nitrous oxide/oxygen, a narrow range of plasma ALFENTA concentrations, approximately 310-340 ng/ml, was shown to provide adequate anesthesia for intra-abdominal surgery, while lower concentrations, approximately 190 ng/ml, blocked responses to skin closure. Plasma concentrations between 100-200 ng/ml provided adequate anesthesia for superficial surgery.

ALFENTA has an immediate onset of action. At dosages of approximately 105 μg/kg, ALFENTA produces hypnosis as determined by EEG patterns; an anesthetic ED_{90} of 182 μg/kg for ALFENTA in unpremedicated patients has been determined, based upon the ability to block response to placement of a nasopharyngeal airway. Based on clinical trials, induction dosage requirements range from 130-245 μg/kg. For procedures lasting 30-60 minutes, loading dosages of up to 50 μg/kg produce the hemodynamic responses to endotracheal intubation and skin incision comparable to those from fentanyl. A pre-intubation loading dose of 50-75 μg/kg prior to a continuous infusion attenuates the response to laryngoscopy, intubation and incision. Subsequent administration of ALFENTA infusion administered at a rate of 0.5-3.0 μg/kg/min with nitrous oxide/oxygen attenuates sympathetic responses to surgical stress with more rapid recovery than enflurane.

Requirements for volatile inhalation anesthetics were reduced by thirty to fifty percent during the first 60 minutes of maintenance in patients administered anesthetic doses (above 130 μg/kg) of ALFENTA as compared to patients given doses of 4-5 mg/kg thiopental for anesthetic induction. At anesthetic induction dosages, ALFENTA provides a deep level of anesthesia during the first hour of anesthetic maintenance and provides attenuation of the hemodynamic response during intubation and incision.

Following an anesthetic induction dose of ALFENTA, requirements for ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance.

Patients with compromised liver function and those over 65 years of age have been found to have reduced plasma clearance and extended terminal elimination for ALFENTA, which may prolong postoperative recovery.

Bradycardia may be seen in patients administered ALFENTA. The incidence and degree of bradycardia may be more pronounced when ALFENTA is administered in conjunction with non-vagolytic neuromuscular blocking agents or in the absence of anticholinergic agents such as atropine.

Administration of intravenous diazepam immediately prior to or following high doses of ALFENTA has been shown to produce decreases in blood pressure that may be secondary to vasodilation; recovery may also be prolonged.

Patients administered doses up to 200 μg/kg of ALFENTA have shown no significant increase in histamine levels and no clinical evidence of histamine release.

Skeletal muscle rigidity is related to the dose and speed of administration of ALFENTA. Muscular rigidity will occur with an immediate onset following anesthetic induction dosages. Preventative measures (see WARNINGS) may reduce the rate and severity.

The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Although higher doses may produce apnea and a longer duration of respiratory depression, apnea may also occur at low doses.

INDICATIONS AND USAGE

ALFENTA (alfentanil hydrochloride) is indicated:

- as an analgesic adjunct given in incremental doses in the maintenance of anesthesia with barbiturate/nitrous oxide/oxygen.
- as an analgesic administered by continuous infusion with nitrous oxide/oxygen in the maintenance of general anesthesia.
- as a primary anesthetic agent for the induction of anesthesia in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required.

SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF ALFENTA.

CONTRAINDICATIONS

ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS.

AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE.

BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY.

ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 μg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 μg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to ¼ of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 μg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 μg/kg).

The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS

DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.

General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight.

In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients.

In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged.

Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction.

Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery.

Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods.

The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent.

Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance.

Administration of ALFENTA infusion should be discontinued at least 10-15 minutes prior to the end of surgery.

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.

Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction.

Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.

Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits.

There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.

Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 μg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.

Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.

ADVERSE REACTIONS

The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported.

The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

	ALFENTA (N=785) %	Fentanyl (N=243) %	Thiopental Sodium (N=66) %	Enflurane (N=55) %	Halothane (N=18) %	Saline Placebo* (N=18) %
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were:

Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching.

Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.

DRUG ABUSE AND DEPENDENCE

ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE

Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD_{50} of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression.

The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

DOSAGE AND ADMINISTRATION

The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

See Dosage Chart for the use of ALFENTA: 1) by incremental injection as an analgesic adjunct to anesthesia with barbiturate / nitrous oxide / oxygen for short surgical procedures (expected duration of less than one hour); 2) by continuous infusion as a maintenance analgesic with nitrous oxide / oxygen for general surgical procedures; and 3) by intravenous injection in anesthetic doses for the induction of anesthesia for general surgical procedures with a minimum expected duration of 45 minutes.

Usage in Children: Clinical data to support the use of ALFENTA in patients under 12 years of age are not presently available. Therefore, such use is not recommended.

Premedication: The selection of preanesthetic medications should be based upon the needs of the individual patient.

Neuromuscular Blocking Agents: The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS sections).

In patients administered anesthetic (induction) dosages of ALFENTA, it is essential that qualified personnel and adequate facilities are available for the management of intraoperative and postoperative respiratory depression.

Also see WARNINGS and PRECAUTIONS sections.

For purposes of administering small volumes of ALFENTA accurately, the use of a tuberculin syringe or equivalent is recommended.

The physical and chemical compatibility of ALFENTA have been demonstrated in solution with normal saline, 5% dextrose in normal saline, 5% dextrose in water and Lactated Ringers. Clinical studies of ALFENTA infusion have been conducted with ALFENTA diluted to a concentration range of 25 µg/ml to 80 µg/ml.

As an example of the preparation of ALFENTA for infusion, 20 ml of ALFENTA added to 230 ml of diluent provides a 40 µg/ml solution of ALFENTA.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

DOSAGE RANGE CHART

Indication	Incremental Injection	Incremental Injection	Continuous Infusion*	Anesthetic Induction
Approximate Duration of Anesthesia	≤ 30 mins	30-60 mins	> 45 mins	> 45 mins
Induction Period (Initial Dose)	8-20 µg/kg	20-50 µg/kg	50-75 µg/kg	130-245 µg/kg
Maintenance Period (Increments/ Infusion)	3-5 µg/kg or 0.5-1 µg/kg/min	5-15 µg/kg	0.5-3.0 µg/kg/min Average Infusion Rate 1-1.5 µg/kg/min	0.5 to 1.5 µg/kg/min or general anesthetic
Total Dose	8-40 µg/kg	up to 75 µg/kg	dependent on duration of procedure	dependent on duration of procedure
Effects	Spontaneously breathing or assisted ventilation when required.	Assisted or controlled ventilation required. Attenuation of response to laryngoscopy and intubation.	Assisted or controlled ventilation required. Some attenuation of response to intubation and incision, with intraoperative stability.	Assisted or controlled ventilation required. Administer slowly (over three minutes). Concentration of inhalation agents reduced by 30-50% for initial hour.

INFUSION DOSAGE

***Continuous Infusion:** 0.5-3.0 µg/kg/min administered with nitrous oxide / oxygen in patients undergoing general surgery. Following an anesthetic induction dose of ALFENTA, infusion rate requirements are reduced by 30-50% for the first hour of maintenance.

Changes in vital signs that indicate a response to surgical stress or lightening of anesthesia may be controlled by increasing the rate up to a maximum of 4.0 µg/kg/min and/or administration of bolus doses of 7 µg/kg. If changes are not controlled after three bolus doses given over a five minute period, a barbiturate, vasodilator, and/or inhalation agent should be used. Infusion rates should always be adjusted downward in the absence of these signs until there is some response to surgical stimulation.

Rather than an increase in infusion rate, 7 µg/kg bolus doses of ALFENTA or a potent inhalation agent should be administered in response to signs of lightening of anesthesia within the last 15 minutes of surgery. Administration of ALFENTA infusion should be discontinued at least 10-15 minutes prior to the end of surgery.

HOW SUPPLIED

Each ml of ALFENTA (alfentanil hydrochloride) Injection for intravenous use contains alfentanil hydrochloride equivalent to 500 µg of alfentanil base. ALFENTA Injection is available as:

NDC 50458-060-02, 2 ml ampoules in packages of 10
NDC 50458-060-05, 5 ml ampoules in packages of 10
NDC 50458-060-10, 10 ml ampoules in packages of 5
NDC 50458-060-20, 20 ml ampoules in packages of 5

Protect from light. Store at room temperature 15°-30°C (59°-86°F).
U.S. Patent No. 4,167,574 March 1987 49-7619901-M

Manufactured by Taylor Pharmacal Co. for

JANSSEN
PHARMACEUTICA
Piscataway, NJ 08854

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Effects of Cyclosporine on Anesthetic Action

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CIRELLA VN, PANTUCK CB, LEE YJ, PANTUCK EJ. Effects of cyclosporine on anesthetic action. Anesth Analg 1987;66:703–6.

The effects of a single dose of cyclosporine on anesthetic actions of pentobarbital and fentanyl were studied in mice. Mice given pentobarbital 2 hr after receiving cyclosporine, 60 mg/kg, slept a statistically significant 2.3 times longer than did controls. In a second study, each of two dose levels of cyclosporine was given before each of four dose levels of fentanyl. The analgesic effect of fentanyl, measured with the abdominal constriction test, was dose-dependent. Cyclosporine significantly increased the analgesia produced by fentanyl and did so in a dose-dependent manner. Cyclosporine by itself did not produce analgesia. Plasma levels of fentanyl and binding of fentanyl by plasma proteins were unchanged by cyclosporine treatment. The results show that a single dose of cyclosporine can increase pentobarbital hypnosis and fentanyl analgesia in mice but do not establish the mechanism of these interactions.

Key Words: IMMUNE RESPONSE, SUPPRESSION—cyclosporine. INTERACTIONS (DRUG)—cyclosporine, anesthetics.

The discovery of cyclosporine, a highly effective immunosuppressant, has revolutionized the field of transplantation. This derivative of a fungus has increased the success rate of liver, kidney, and heart transplantations dramatically. Unfortunately, this success has not come without problems. The side effects of cyclosporine include renal toxicity, hepatic toxicity, and possible tumorigenicity. It has been our impression that many patients undergoing transplantation procedures at our institution take considerably longer to recover from anesthesia than we would have anticipated. Our transplantation patients typically receive a single dose of cyclosporine 1–2 hr before being brought to the operating room. In this study, we have examined the effects of administration of a single dose of cyclosporine on pentobarbital sleep time and on fentanyl analgesia in mice. In addition, we have examined the effects of cyclosporine on plasma concentrations and plasma protein binding of fentanyl.

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Methods

Animals

Male CD-1 mice, 20–30 g (Charles River Laboratories, Wilmington, MA), were used for all experiments. They were housed in plastic cages with corn cob bedding and allowed food and water ad libitum. Institutional guidelines for the care and use of animals were followed.

Effect of Cyclosporine on Pentobarbital Sleep Time

Nineteen mice were given cyclosporine (Sandimmune IV, Sandoz Pharmaceuticals, East Hanover, NJ), 60 mg/kg, and 18 mice the equivalent volume of vehicle intramuscularly (IM). Comparable doses have been used in studies employing cyclosporine to produce immunosuppression in mice (1,2). Two hours later, the animals were given sodium pentobarbital intraperitoneally (IP), 50 mg/kg, and sleep time, defined as time from loss to return of righting reflex, was measured. Results were analyzed by Student's unpaired t-test and considered statistically significant if $P < 0.05$.

Effect of Cyclosporine on Fentanyl Analgesia

Mice were given cyclosporine, 30, 60, or 90 mg/kg, or vehicle IM. Two hours later, subgroups consisting of

Table 1. Effect of Cyclosporine on Pentobarbital Sleep Time

Treatment	Sleep time (min)
Control	30.4 ± 3.2
Cyclosporine	70.4 ± 4.2[a]

Male CD-1 mice weighing approximately 25 g were injected with vehicle or cyclosporine, 60 mg/kg IM. Two hours later they were given sodium pentobarbital, 50 mg/kg IP.

Values are mean ± SEM for 18–19 mice.

[a]Statistically different from control using Student's unpaired t-test.

Table 2. Effect of Cyclosporine on Writhing

Dose of cyclosporine (mg/kg)	Writhes (number/5 min)
0	54.3 ± 3.6
30	45.0 ± 1.8
60	47.8 ± 1.6
90	47.2 ± 2.2

Male CD-1 mice weighing approximately 25 g were given vehicle or cyclosporine IM. The abdominal constriction test was performed 2 hr later. Each value is the mean ± SEM for 6–11 groups of five mice.

One-way ANOVA showed no significant effect of cyclosporine.

at least 25 mice each from the 30-mg, 60-mg, and vehicle treatment groups were given one of four doses of fentanyl citrate, 10, 15, 20, or 25 μg/kg, or vehicle IM. The 90-mg cyclosporine treatment group, which consisted of 30 animals, was given fentanyl vehicle only. Analgesia was then assessed using the abdominal constriction test (3). Five minutes after the dose of fentanyl, 0.5 ml of 1% acetic acid was injected IP, and 10 min later the number of abdominal constrictions, or writhes, was counted for 5 min by a blinded observer. Five mice were studied at a time. Percent analgesia was defined as the following: [(mean writhes per 5 min in control group − mean writhes per 5 min in treated group)/(mean writhes per 5 min in control group)] × 100. Statistical significance of differences among groups was assessed by two-way analysis of variance. The cyclosporine effect was further broken into two orthogonal components, linear and quadratic. Effects were considered significant if $P < 0.05$.

Effect of Cyclosporine on Plasma Concentrations of Fentanyl

Forty-eight mice were given cyclosporine, 60 mg/kg IM, and 48 were treated IM with cyclosporine vehicle. Two hours later, the mice were given fentanyl, 20 μg/kg IM. Five, 10, 15, 20, 30, 45, 60, and 90 min after fentanyl administration, six mice were anesthetized for 20–30 sec with diethyl ether and were exsanguinated by vena caval puncture. Heparinized blood was centrifuged and plasma separated and stored at −20°C until analysis. Plasma concentrations of fentanyl were determined by radioimmunoassay (RIA-Kit Fentanyl, Janssen Pharmaceuticals). Results were evaluated using two-way analysis of variance and considered statistically significant if $P < 0.05$.

Effect of Cyclosporine on Binding of Fentanyl by Plasma Proteins

Thirty mice were treated with cyclosporine, 60 mg/kg IM, and 30 mice were treated with cyclosporine vehicle IM. Two hours later, after 20–30 sec of ether anesthesia, the mice were exsanguinated by vena caval puncture. Heparinized blood was then centrifuged and plasma separated and stored at −20°C until used for binding assays. Plasma from two or three mice was combined to form a total of thirteen pools of plasma from cyclosporine-treated mice and thirteen pools of plasma from control mice. Equilibrium dialyses were carried out using a Spectrum Equilibrium Dialyzer (Spectrum Medical Industries, Los Angeles, CA) with lucite cells whose halves were separated by a semipermeable cellulose membrane with a molecular weight cutoff of 12,000–14,000 (Fisher Scientific, Pittsburgh, PA). Tritiated fentanyl (13.2 Ci/mmol, Janssen Pharmaceuticals) diluted with nonradioactive fentanyl was added to plasma, 0.2 ml, and dialyzed against an equal volume of 0.1M phosphate buffer pH 7.4. The cells were rotated 13 times/min for 2 hr in a 37°C water bath. Aliquots (100 μl) were taken from each side of the membrane and the radioactivity determined in a Packard Model 300 Tri-Carb Liquid Scintillation Spectrometer (Packard Instruments Co., Downers Grove, IL) with automatic external standard quench correction. Results were analyzed by Student's unpaired t-test and considered statistically significant if $P < 0.05$.

Results

Cyclosporine-treated mice slept a significant 2.3 times longer after the administration of sodium pentobarbital than did control animals (Table 1). Cyclosporine treatment alone did not alter control levels of writhing (Table 2). Percent analgesia increased significantly with increasing doses of fentanyl (Fig. 1). Cyclosporine significantly increased the analgesia produced by fentanyl and did so in a dose-dependent manner (Fig. 1). The linear component of the effect of cyclosporine was significant, the quadratic component was not significant, and the interaction term of the analysis of variance was not significant, showing that the effect of increasing doses of cyclosporine on percent anal-

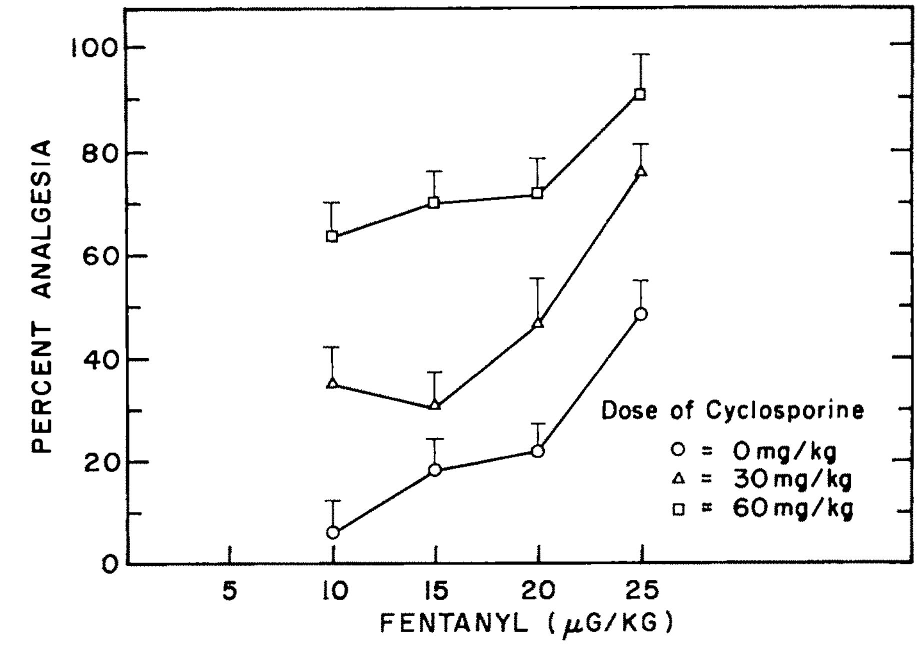

Figure 1. Effect of cyclosporine on fentanyl analgesia. Male CD-1 mice weighing approximately 25 g were given cyclosporine or vehicle IM. Two hours later they were given fentanyl citrate or vehicle IM. The abdominal constriction test was performed 5 min after the dose of fentanyl. Each point is the mean ± SEM for 5–11 groups of five mice. Two-way ANOVA showed that percent analgesia increased significantly with increasing doses of fentanyl and with increasing doses of cyclosporine.

Figure 2. Effect of cyclosporine on plasma levels of fentanyl. Male CD-1 mice weighing approximately 25 g were given cyclosporine, 60 mg/kg, or vehicle IM. Two hours later they were given fentanyl citrate, 20 µg/kg IM. Each point is the mean ± SEM for six mice. Two-way ANOVA showed no statistically significant differences in plasma levels of fentanyl between control and cyclosporine-treated mice.

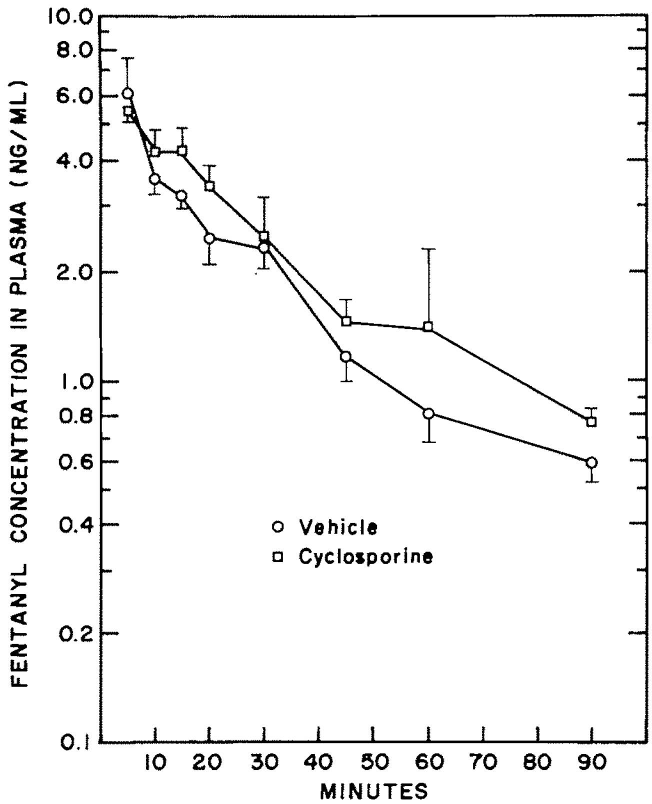

Table 3. Effect of Cyclosporine on Binding of Fentanyl by Plasma Proteins

Group	Percent binding
Control	68.6 ± 1.3
Cyclosporine-treated	65.1 ± 1.5

Plasma was obtained from male CD-1 mice weighing approximately 25 g and treated 2 hr previously with cyclosporine, 60 mg/kg, or vehicle IM. In each group, 13 pools of plasma were used to measure fentanyl binding. Each pool consisted of plasma from 2–3 mice.

The difference in binding between plasma from control and cyclosporine-treated mice was not statistically significant using Student's unpaired *t*-test.

gesia was consistent across all doses of fentanyl. There were no significant differences between cyclosporine-treated mice and control mice in the concentrations of fentanyl in plasma (Fig. 2). There also was no significant difference in binding of fentanyl by proteins in plasma from control and from cyclosporine-treated mice (Table 3).

Discussion

Our data show that previous treatment of mice with a single dose of cyclosporine increases the hypnotic effect of pentobarbital and the analgesic effect of fentanyl. However, the mechanism of these interactions is not clear. Studies in rodents (4–6) have shown that a single dose of cyclosporine selectively inhibits the oxidative metabolism of substrates by cytochrome P450 enzymes. However, our data do not support inhibition of cytochrome P450 as the reason for the en-

hanced analgesic action of fentanyl that we observed in cyclosporine-treated mice, as plasma levels of fentanyl in the cyclosporine-treated animals were not different from those in control animals. Because we also did not find any alteration in binding of fentanyl by plasma proteins in cyclosporine-treated animals, our study suggests that the increased effect of fentanyl in these animals may be the result of a pharmacodynamic interaction rather than a pharmacokinetic one, though the latter possibility has not been ruled out. The effects of cyclosporine treatment of mice on brain tissue levels of subsequently administered fentanyl and on brain opiate receptor binding characteristics for fentanyl need to be examined.

Recently Gramstad et al. (7) have shown that in cats a single dose of cyclosporine enhances neuromuscular blockade by vecuronium and by atracurium, and Dougherty et al. (8) have shown that in rats the analgesic effect of morphine, measured using a hot water tail immersion test, is inhibited by a single dose of cyclosporine. It is of interest that we and Dougherty et al. found opposite effects on analgesia of cyclosporine administered 2 hr before a narcotic. We do not know whether this difference in direction of effect derives from differences between properties of fentanyl and morphine or from differences between the two studies in methodology such as technique used to measure analgesia. As in our study, neither the investigation by Gramstad et al. nor that by Dougherty et al. identified the mechanisms of the observed drug interactions; thus it is not possible at present to predict whether or in what fashion cyclosporine might influence the activity of other drugs. Anesthesiologists should be alert to the possibility that the action of drugs may be altered in individuals receiving even a single dose of cyclosporine.

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Ventilatory Response to Carbon Dioxide after Intramuscular and Epidural Fentanyl

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NEGRE I, GUENERON J-P, ECOFFEY C, PENON C, GROSS JB, LEVRON J-C, SAMII K. Ventilatory response to carbon dioxide after intramuscular and epidural fentanyl. Anesth Analg 1987;66:707–10.

The authors compared the effects of administration of fentanyl 200 μg on the ventilatory response to carbon dioxide in two groups of nine healthy unpremedicated subjects: one group received fentanyl as an intramuscular injection; in the other group, fentanyl was injected into the epidural space. In the intramuscular group, the slope of the ventilatory response to CO_2 did not decrease significantly. In the epidural group, the slope of the ventilatory response to CO_2 decreased significantly from 2.48 ± 1.05 to 1.77 ± 0.7, 1.74 ± 0.7, and 2.07 ± 0.74 L·min^{-1}·mm Hg^{-1} at 30, 60, and 120 min after injection (x ± SD, $P \leq 0.05$), respectively. At each time of the study, plasma fentanyl levels were significantly lower in the epidural group than in the intramuscular group ($P \leq 0.05$). These results suggest that epidural fentanyl induces a nonsystemic ventilatory depression that may be due to the rostral spread of the drug.

Key Words: ANALGESIA, NARCOTIC—fentanyl. ANESTHETIC TECHNIQUES—epidural, intramuscular. VENTILATION—carbon dioxide response.

Epidural opioids are effective for the treatment of postoperative pain. One of the main side effects of this technique is respiratory depression (1). Indeed, morphine given epidurally sometimes provokes a delayed and prolonged depression of the ventilatory control (2) that may be attributed to rostral spread of this water-soluble opioid (3). It has been suggested that a more lipid soluble drug, such as fentanyl, could provide more segmentalized analgesia without spread of the drug to the brain (3), which is in agreement with the absence of delayed respiratory depression (4). Lomessy et al. showed that fentanyl 200 μg given epidurally provides effective postoperative analgesia without significant respiratory depression (5). However, they only measured resting respiratory rate and Pa_{CO_2}, which are not sensitive enough to ensure that adequate ventilation will be maintained. The goal of our study was to compare the effects of epidural or intramuscular fentanyl 200 μg on the ventilatory response to CO_2.

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Methods

Patients

The study protocol received institutional approval, and informed consent was obtained from all participants. None of them had clinical evidence of respiratory, cardiovascular, hepatic, or CNS disorder and none received any medication before the study or took caffeine or alcohol-containing beverages. Subjects were not premedicated and fasted overnight. They did not smoke before the study. Two groups were studied: the epidural group consisted of nine ASA I males scheduled for minor orthopedic (arthroscopy) or urologic (lithotripsy) procedures. Mean (±SD) age, weight, and height were 29 ± 5 yr, 70 ± 9 kg, 176 ± 8 cm, respectively. The intramuscular group consisted of nine ASA I male volunteers. Mean (±SD) age, weight, and height were 25 ± 2 yr, 69 ± 7 kg, 177 ± 4 cm, respectively.

Procedure For Epidural Injection

An infusion of Ringer's lactate solution was begun (3 ml·kg^{-1}·hr^{-1}) through a 16-g venous catheter and atropine 0.5 mg was administered intravenously. A 16-g closed venous catheter was inserted in the other arm for blood samples. The ECG was continuously

Table 1. Respiratory Variables and Plasma Fentanyl Values Before and after Intramuscular and Epidural Fentanyl (200 μg) (Mean Values ± SD)

	Control	Minutes after fentanyl administration			
		30	60	120	180
Resting $P_{ET_{CO_2}}$ (mm Hg)					
IM	37.8 ± 3.9	39.9 ± 5.2	38.8 ± 4.1	39.4 ± 3.2	38.3 ± 3.9
Epidural	34.7 ± 3.2	37.6 ± 6.9	37.1 ± 5.0	37.1 ± 5.5	34.8 ± 5.3
Resting RR (Breaths/min)					
IM	13 ± 2	14 ± 2	15 ± 3	14 ± 3	15 ± 4
Epidural	14 ± 4	14 ± 5	13 ± 5	14 ± 3	14 ± 4
Resting $\dot{V}_E$ (L/min)					
IM	9.3 ± 2.2	9.3 ± 4.1	9.5 ± 4.6	8.4 ± 2.2	8.3 ± 1.9
Epidural	9.3 ± 4.5	8.4 ± 4.4	7.9 ± 3.0	8.5 ± 3.2	9.2 ± 3.0
Slope $\dot{V}_E/P_{ET_{CO_2}}$ ($L/min^{-1} \cdot mm\ Hg^{-1}$)					
IM	2.43 ± 0.72	1.86 ± 0.94	1.93 ± 0.57	2.15 ± 0.88	2.23 ± 0.81
Epidural	2.48 ± 1.05	1.77 ± 0.70[a]	1.74 ± 0.70[a]	2.07 ± 0.74[a]	2.11 ± 0.63
Plasma Fentanyl (ng/ml)					
IM	—	0.93 ± 0.38	0.85 ± 0.26	0.69 ± 0.21	0.64 ± 0.14
Epidural	—	0.50 ± 0.15[b]	0.54 ± 0.19[b]	0.47 ± 0.12[b]	0.43 ± 0.07[b]

Abbreviations: $P_{ET_{CO_2}}$, end tidal tension CO_2; RR, respiratory rate; $\dot{V}_E$, minute ventilation.
[a] $P \leq 0.05$ from control value.
[b] $P \leq 0.05$ from IM value.

displayed on an electrocardioscope and arterial blood pressure was measured by sphygmomanometry. With patients in a sitting position, we used a 17-g Tuohy needle to insert an epidural catheter at the L3–L4 interspace; we advanced the catheter until the 10-cm mark was at skin level. Through the catheter we then injected 3 ml of lidocaine 2% with epinephrine 1:200,000 to rule out intravascular or subarachnoid injection. The patient was then turned supine with a 45-degree head-up tilt. After control measurements, fentanyl 200 μg in 10 ml of saline solution was injected. At 30, 60, 120, and 180 min after fentanyl administration, segmental analgesia was assessed by pinprick. After the study, local anesthetics were injected through the epidural catheter to provide surgical anesthesia. All epidural anesthetics were effective and surgery was carried out without use of other anesthetics.

The volunteers did not receive an IV infusion during the study, but an 18-g closed venous catheter was inserted for plasma fentanyl measurements.

Ventilatory Measurements

In all subjects, a CO_2 ventilatory stimulation test was performed the day before the procedure to familiarize them with the experiment. Results of this test were not included in the data. On the day of the procedure, the ventilatory responses to CO_2 breathing were measured while breathing room air and using Read's rebreathing method (6). All subjects were studied in a 45-degree head-up position. Control values were obtained 15 min after insertion of the epidural catheter in the epidural group, immediately before fentanyl injection in the intramuscular group. The subjects rebreathed CO_2 through a mouthpiece connected to a Fleisch number 2 pneumotachograph. The inspiratory and expiratory circuits were separated by a Rudolph valve. Resistance to inspiratory and expiratory flow was 2.4 and 3.6 cm $H_2O \cdot sec^{-1} \cdot L^{-1}$ respectively, at a flow of 1 L/sec. Volume was measured by electronically integrating the flow signal obtained from a Godart 17212 differential pressure transducer (Bilthoven, Holland) connected to the pneumotachograph, which was previously calibrated with a 1-L syringe of air. End-tidal CO_2 tension ($P_{ET_{CO_2}}$) was measured with a Godart capnograph (Bilthoven, Holland) that was calibrated before and after each measurement with 5 and 7% CO_2 in O_2 from calibrated tanks, which were verified to be accurate within 1% of the assigned value using Micro Scholander analysis. All signals were recorded on a Gould ES 1000 recorder using a paper speed of 10-mm/sec. Total cycle duration was measured from the flow signal. Tidal volume (V_T) was measured by integrating the flow signal. Respiratory rate (RR) and minute ventilation ($\dot{V}_E$) were calculated from these values by analyzing and averaging three breaths at 30-sec intervals.

During air breathing, we found that a steady state was obtained after 5 min, with stabilization of $P_{ET_{CO_2}}$ values; all resting values presented represent

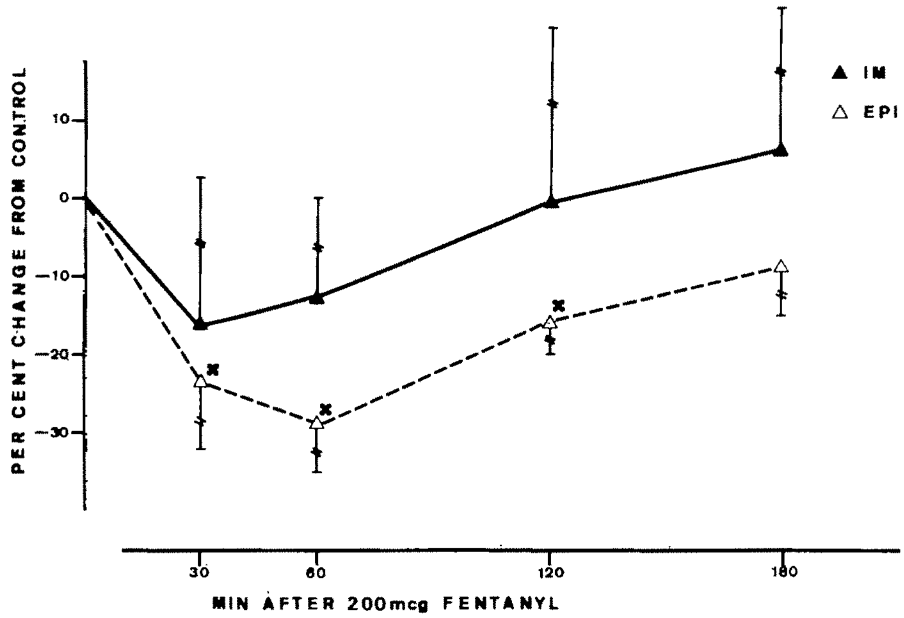

Figure 1. Percentage of change from control value in the slope $\dot{V}E/PET_{CO_2}$ after administration of fentanyl (200 μg) intramuscularly (▲) or epidurally (△). Mean ± SEM. $P \leq 0.05$ from control value.

the means of ten breaths obtained at this time. Furthermore, subjects breathed from a 7-L bag initially filled with 7% CO_2 in O_2; measurements from the first 30–40 sec were discarded until a linear rising PET_{CO_2} phase was observed; this began when PET_{CO_2} was approximately 50 mm Hg. For each of the subsequent 3–4 min, PET_{CO_2} and $\dot{V}E$ were calculated at 30-sec intervals. Rebreathing was continued until PET_{CO_2} increased to 70 mm Hg. After converting ventilatory variables to BTPS, we determined the slope of the ventilatory response to CO_2 by least-squares linear regression of $\dot{V}E$ on PET_{CO_2}. All responses were linear, with correlation coefficients (r) ranging between 0.91 and 0.98.

Plasma Fentanyl Analysis

Plasma fentanyl levels were assayed from venous blood samples taken 30, 60, 120, and 180 min after the injection of fentanyl, just before each CO_2 rebreathing test. Plasma was separated by centrifugation at −4°C, stored at −20°C, and assayed in duplicate by radioimmunoassay, which measured fentanyl with a minimum detectable level of 0.1 ng/ml and a coefficient of variation of less than 1% (7).

Statistical Analysis

Differences between respiratory variables at each time interval and control values were tested using ANOVA followed by the use of the *t*-test for paired data. Differences between the two groups were tested with the use of the *t*-test for unpaired data. Differences between the two groups in plasma levels of fentanyl were tested using the nonparametric test of Mann and Whitney. Differences were considered statistically significant when $P \leq 0.05$. All values were expressed as mean ± SD.

Results

Intramuscular Group

Apnea never occurred. Ventilatory variables are summarized in Table 1 and Figure 1. Resting RR, $\dot{V}E$, PET_{CO_2} values and the slope $\dot{V}E/PET_{CO_2}$ did not change significantly from their control values.

Epidural Group

Apnea was never observed and no segmental level of analgesia was found within 3 hr. The results of the ventilatory variables and plasma fentanyl levels are summarized in Table 1 and Figure 1. Epidural fentanyl did not change resting RR, $\dot{V}E$, and PET_{CO_2}. The slope $\dot{V}E/PET_{CO_2}$ was significantly below control values at 30, 60, and 120 min. At 180 min, the slope $\dot{V}E/PET_{CO_2}$ was no longer significantly decreased. However, at 180 min two patients had persistent significant decreases in the slope $\dot{V}E/PET_{CO_2}$ below control values (−38 and −30%). At each time in the study, plasma fentanyl levels were significantly lower in the epidural group than in the intramuscular group.

Discussion

The major finding of this study is that 200 μg epidural fentanyl causes respiratory depression, whereas the

same dose of fentanyl given intramuscularly does not induce any ventilatory change despite significantly higher plasma fentanyl levels. Our 200-μg epidural fentanyl dose is higher than the previously reported doses, which ranged from 80 to 100 μg (8–11).

Recently, a higher dose (200 μg) has been proposed either for potentiation of local anesthetics (12) or for postoperative pain relief (5). On the other hand, Renaud et al. recently reported that a bolus of 1 μg/kg followed by infusion of 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ fentanyl given epidurally induces respiratory depression (13). It was, therefore, important to investigate the effect of such a high dose of fentanyl given epidurally on the control of ventilation measured by the CO_2 rebreathing method. Lomessy et al. previously reported a significant decrease in resting respiratory rate that lasted 1 hr after epidural injection of fentanyl (5). Their study was, however, performed in the postoperative period and pain may have affected their results. Additionally, they did not study the sensitivity to CO_2, which is more accurate for assessing the control of ventilation than are resting respiratory variables alone. The absence of significant respiratory depression in the intramuscular group in the present study is due to scattered individual changes in the ventilatory variables. This absence of change in the control of ventilation is, however, not unexpected since fentanyl plasma levels after intramuscular injection were lower than the 1–2 ng/ml threshold level for ventilatory depression (14).

The respiratory depression observed after epidural fentanyl may be due to three mechanisms alone or in combination: 1) a systemic effect; 2) rostral spread in the CSF (2); and 3) a rostral spread via a direct perimedullary vascular channel (3). A systemic effect seems unlikely. Indeed, 30, 60, and 120 min after epidural administration, plasma fentanyl levels were comparable to those previously reported by Lomessy et al. (5). Levels observed were significantly less than after intramuscular administration of fentanyl. Nonetheless, depression of the slope of the ventilatory response to CO_2 occurred after epidural injection. This suggests that rostral spread of fentanyl may have contributed to the ventilatory depression in the epidural group. This contrasts with the hypothesis that, unlike morphine, fentanyl, a highly lipid soluble opioid, easily crosses the dura, and quickly penetrates the spinal cord, inducing segmental analgesia without the side effects associated with migration of the opioid in a rostral direction (3,12). However, rostral spread of morphine in the CSF is generally delayed, occurring 3 or 4 hr after epidural opioid administration (3). Perhaps fentanyl spreads by different mechanisms than does morphine; one such possibility could be direct rostral spread via a perimedullary vascular channel (3).

In conclusion, epidural fentanyl depresses the control of ventilation as reflection by depression on the ventilatory response to CO_2. It is, therefore, necessary to monitor closely patients given epidural fentanyl.

The authors thank Janssen Laboratories for fentanyl plasma level measurements and Miss Guylaine Rosine for secretarial assistance.

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Pharmacologic Basis of Responses to Midazolam in the Isolated, Cross-Perfused, Canine Right Atrium

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SAEGUSA K, FURUKAWA Y, OGIWARA Y, TAKEDA M, CHIBA S. Pharmacologic basis of responses to midazolam in the isolated, cross-perfused, canine right atrium. 1987;66:711–8.

The effects of midazolam on atrial rate and contractile force in the isolated canine atrium perfused with donor blood were investigated. When midazolam in a dose range of 100–1000 μg was injected directly into the sinus node artery of the isolated atrium, biphasic (negative followed by positive) chronotropic and triphasic (positive, negative followed by positive) inotropic effects were induced. After propranolol or imipramine, the positive chronotropic and the secondary positive inotropic effects were significantly suppressed, but the initial positive inotropic effect was not affected. Tetrodotoxin, atropine, or R05-4864, a selective ligand for peripheral benzodiazepine binding sites, did not modify midazolam-induced effects. When midazolam in a dose of 0.1–1 mg/kg was administered intravenously to the donor dog, monophasic negative chronotropic and inotropic effects in the isolated atrium were observed but were not as prominent. We conclude that midazolam has direct cardiac inhibitory properties including catecholamine release due to a tyramine-like action.

Key Words: HEART—rate, contractility. SYMPATHETIC NERVOUS SYSTEM—catecholamines. HYPNOTICS, BENZODIAZEPINES—midazolam.

Midazolam is a short-acting, water-soluble benzodiazepine used for premedication, sedation, and induction of anesthesia (1–3). Cardiac responses to midazolam have generally been characterized by relatively minor changes in cardiac output (4–6). However, data obtained from an experiment using a modified Langendorff isolated heart preparation have shown that midazolam produces a dose-related depressant effect on myocardial contractility (7). Most anesthetics produce a direct negative inotropic effect, which may in part be compensated for by a release of catecholamines due to reflex sympathetic activation. Although midazolam, like most anesthetics, has an inhibitory effect on the heart, alterations in cardiac function after administration of midazolam have been comparatively mild throughout a wide range of doses (4,8). Therefore, it seems possible that midazolam may also have an effect that can counterbalance its cardiac inhibitory property in addition to reflex-mediated compensatory activities.

In the present study, we analyzed pharmacologically the mechanisms underlying midazolam-induced cardiac effects by means of an isolated canine atrium perfused with donor blood. The largest dose of midazolam administered intravenously in a donor dog was 1 mg/kg, which is at least threefold more than the largest dose used intravenously in clinical practice. Furthermore, we compared the cardiac effects of midazolam with those of another induction agent, ketamine, because we have recently demonstrated that ketamine produces both positive and negative chronotropic and inotropic effects, and that the positive effects were caused by a tyramine-like action in the isolated heart (9).

Methods

Forty-eight donor dogs weighing 9–23 kg were anesthetized with 30 mg/kg of IV sodium pentobarbital and artificially ventilated with room air using a Harvard respirator (model 607). Heparin, 500 USP U/kg, was administered intravenously at the beginning of the perfusion, and 200 USP U/kg was added at 1-hr intervals. The systemic blood pressure of the donor dog was measured from the cannulated right femoral artery with a pressure transducer (Nihon Kohden RP-2), and heart rate was measured with a cardiotacho-

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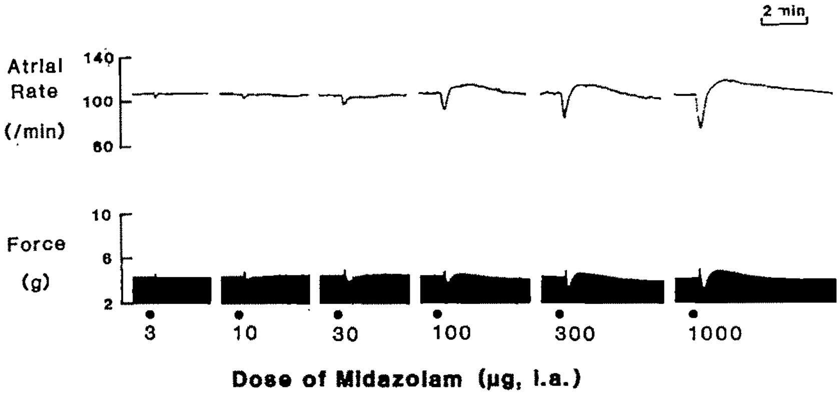

Figure 1. Changes in atrial rate and contractile force produced by midazolam in doses of 3, 10, 30, 100, 300, or 1000 μg injected into the sinus node artery of an isolated, blood-perfused canine atrium.

graph triggered by the R wave of electrocardiographic lead II.

Isolated right atrial preparations were obtained from 48 other mongrel dogs weighing 7–18 kg. Each dog was anesthetized with sodium pentobarbital, 30 mg/kg IV. After treatment with 200 USP U/kg of IV sodium heparin, the right atrium was excised and plunged into a cold Tyrode solution at 4–10°C. The mean wet weight of the atrial preparation was 8.3 g (n = 48). The sinus node artery was cannulated via the right coronary artery and perfused with heparinized blood from the common carotid artery of the donor dog by means of a peristaltic pump (Harvard Apparatus, model 1210). A pneumatic resistance was placed in parallel with the perfusion system so that the perfusion pressure could be maintained constant at 100 mm Hg. Blood flow to the isolated atrium was 3–9 ml/min.

The ventricular margin of the isolated atrium was fixed to a stainless steel bar and placed in a cup-shaped glass container kept at 37°C. The atrium was stretched a resting tension of 2 g. The isometric tension was recorded on a thermowriting rectigraph (Nihon Kohden, WT 685G). A pair of silver electrodes, with an interelectrode distance of 1.5 mm, was brought into contact with the epicardial surface of the isolated atrium to record the electrogram. The atrial rate was derived from the atrial electrogram with a cardiotachometer (Nihon Kohden, AT 600G). Details of this preparation have been described previously (10,11).

Chemicals used in this study were as follows: midazolam maleate and R05-4864, a compound with high affinity for the peripheral benzodiazepine binding sites (12,13) (Nippon Roche, Kamakura, Japan); ketamine hydrochloride and d,1-norepinephrine hydrochloride (NE) (Sankyo, Tokyo, Japan); tyramine hydrochloride, atropine sulphate and dimethylsulfoxide (Wako Purechemical Ind., Osaka, Japan); d,1-propranolol hydrochloride (Sigma Chemical Co., St. Louis, MO, USA); imipramine hydrochloride (Fujisawa, Osaka, Japan); tetrodotoxin (TTX) (Sankyo Central Laboratories, Tokyo, Japan); nicotine (base) (Yamanouchi, Tokyo, Japan); and acetylcholine chloride (ACh) (Daiichi, Tokyo, Japan).

In order to rule out a sinus bradycardia caused by the increase in blood flow, R05-4864 was dissolved in dimethylsulfoxide (14) and then diluted in physiologic saline prior to the start of the experiment. A small volume (0.01 ml) of dimethylsulfoxide solution readily dissolved a large dose (1000 μg) of R05-4864, and the vehicle produced slight negative chronotropic and inotropic effects. Other drugs were dissolved in physiologic saline before starting the experiments. Drugs were injected into the sinus node artery of the isolated atrium through a rubber tube with a microsyringe (Terumo Co.) or administered into the external jugular vein of the donor dog. The amount of drug solution injected with the microsyringe was 0.01–0.03 ml in a period of 4 sec. There were no changes in atrial rate and contractile force when 0.01–0.03 ml of physiologic saline was injected into the sinus node artery in a period of 4 sec.

Data are given as percentage changes in a maximum positive or negative direction. Data collected before and after treatment with a drug were analyzed by paired t-tests.

Results

Chronotropic and Inotropic Actions of Intraarterial Injections of Midazolam in Isolated Atria

Midazolam was injected into the cannulated sinus node artery of the isolated atrium in doses ranging from 3–1000 μg. Three micrograms of midazolam injected into the sinus node artery produced negative chronotropic and slight positive inotropic responses. Ten to 30 μg of midazolam induced negative chronotropic and transient positive followed by negative inotropic responses. In doses of 100–1000 μg, midazolam produced biphasic (i.e., negative followed by

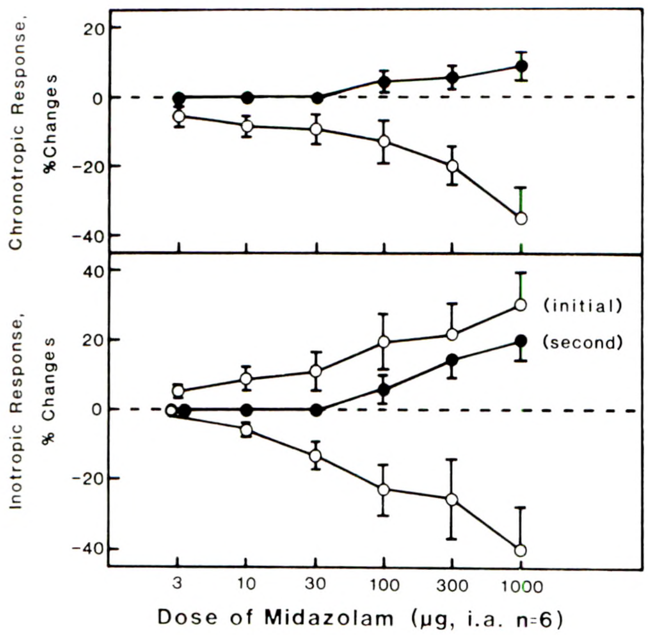

Figure 2. Dose–response curves as percentage changes in the maximum positive or negative chronotropic (upper panel) and inotropic (lower panel) responses to midazolam. Points represent means and vertical lines show SEM. Baseline levels of atrial rate and contractile force in the six isolated atria were 104 ± 5 (mean ± SEM) beats/min and 2.7 ± 0.6 g, respectively. The initial peak positive inotropic response to midazolam seen at all doses is defined as "initial" and the second peak positive inotropic responses seen at doses of 100 μg and above as "second."

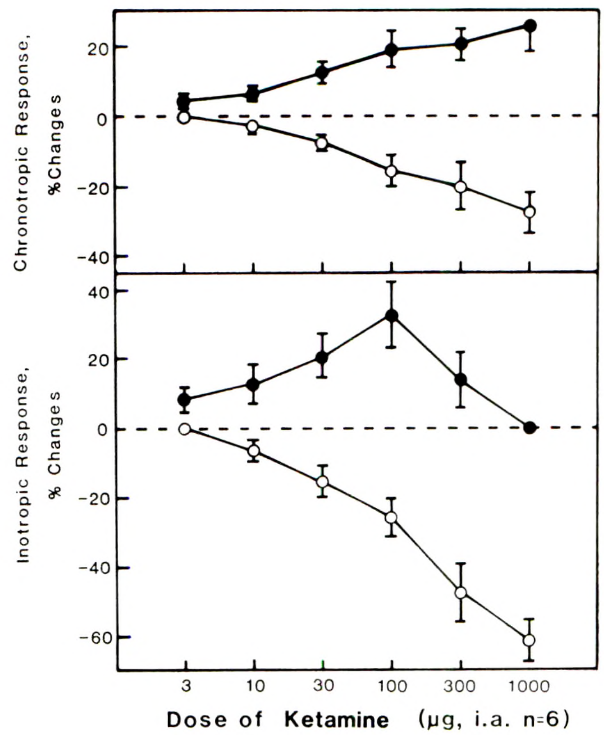

Figure 3. Dose–response curves as percentage changes in the maximum positive or negative chronotropic (upper panel) and inotropic (lower panel) responses to ketamine. Using doses similar to those used with midazolam, ketamine was injected into the sinus node artery of the isolated, blood-perfused, canine atrium. Points represent means and vertical lines show SEM. Baseline levels of atrial rate and contractile force in the six isolated atria were 101 ± 4 (mean ± SEM) beats/min and 2.8 ± 0.4 g, respectively.

positive) chronotropic and triphasic (i.e., positive, negative followed by positive) inotropic responses. Figure 1 shows chronotropic and inotropic effects of increasing doses of midazolam. In Figure 2, dose–response curves in six preparations are summarized in which the chronotropic and inotropic effects of midazolam were evaluated. For comparative purposes, similar doses of ketamine were injected into the sinus node artery of the isolated atrium (Fig. 3). Unlike midazolam, 3 μg ketamine caused small positive chronotropic and inotropic responses. Ten to 300 μg of ketamine induced biphasic (i.e., negative followed by positive) chronotropic and inotropic responses. At 1000 μg, ketamine produced biphasic chronotropic and only negative inotropic responses. Figure 3 shows dose–response curves obtained in the six preparations in which the chronotropic and inotropic effects of ketamine were studied.

Pharmacologic Basis of Positive Chronotropic and Inotropic Responses to Midazolam

A large dose of midazolam (1000 μg) produced clearly biphasic chronotropic and triphasic inotropic effects (Figs. 1 and 2). The initial positive inotropic response to midazolam was not affected by pretreatment with a β-adrenoceptor blocking agent, propranolol. On the other hand, the positive chronotropic and the secondary positive inotropic responses were suppressed by propranolol treatment that blocked norepinephrine (NE)-induced positive chronotropic and inotropic responses as shown in Figure 4. The duration of negative chronotropic and inotropic responses to midazolam (>30 μg) were prolonged by propranolol. Data summarizing five experiments are shown in Figure 5. Effects of imipramine, a drug that inhibits neuronal uptake of NE, on the cardiac responses to midazolam, NE, and tyramine are summarized in Figure 6. Three hundred micrograms of imipramine significantly suppressed the positive chronotropic and the secondary positive inotropic responses to 1000 μg of midazolam ($P < 0.05$ and $P < 0.01$, respectively). The positive chronotropic and inotropic responses to 3 μg of tyramine were also significantly inhibited by 300 μg of imipramine ($P < 0.05$ and $P < 0.01$, respectively). The same dose of imipramine significantly potentiated the positive chronotropic and inotropic responses to 0.03

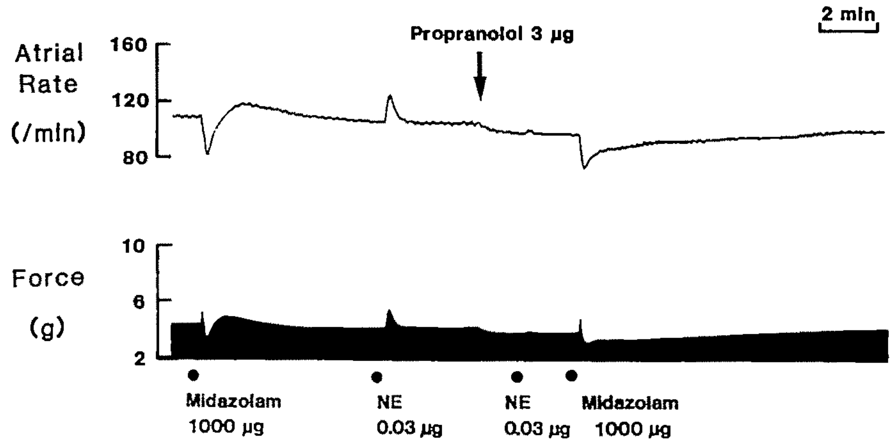

Figure 4. Effects of propranolol on responses of atrial rate and contractile force to midazolam and norepinephrine (NE) in an isolated, blood-perfused, canine atrium. One thousand micrograms of midazolam, 0.03 μg of NE, and 3 μg of propranolol were injected into the sinus node artery.

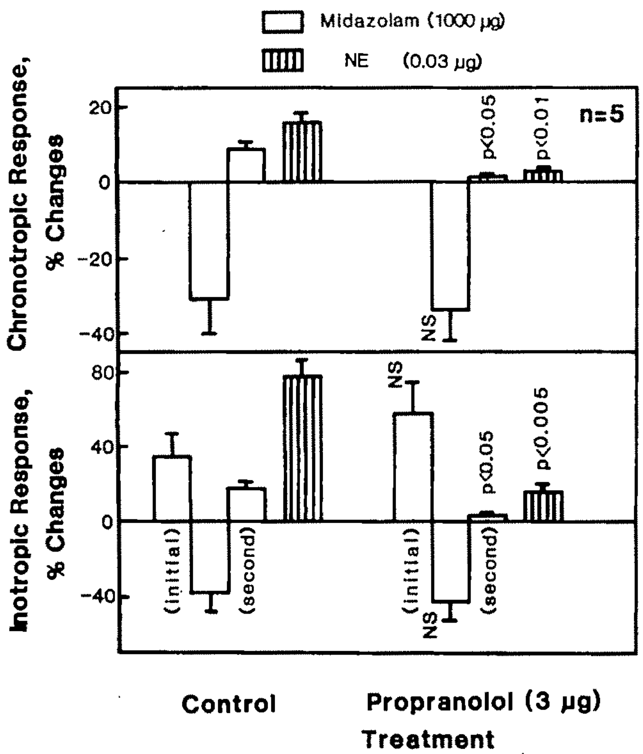

Figure 5. Effects of 3 μg of propranolol on the percentage changes in chronotropic and inotropic responses associated with 1000 μg of midazolam and 0.03 μg of norepinephrine (NE) in five isolated atria. Vertical lines show SEM. Comparisons are with control values (paired t-test); NS means no statistical significance ($P > 0.05$). Baseline levels of atrial rate and contractile force in the five atria were 105 ± 5 (means ± SEM) beats/min and 2.5 ± 0.3 g, respectively.

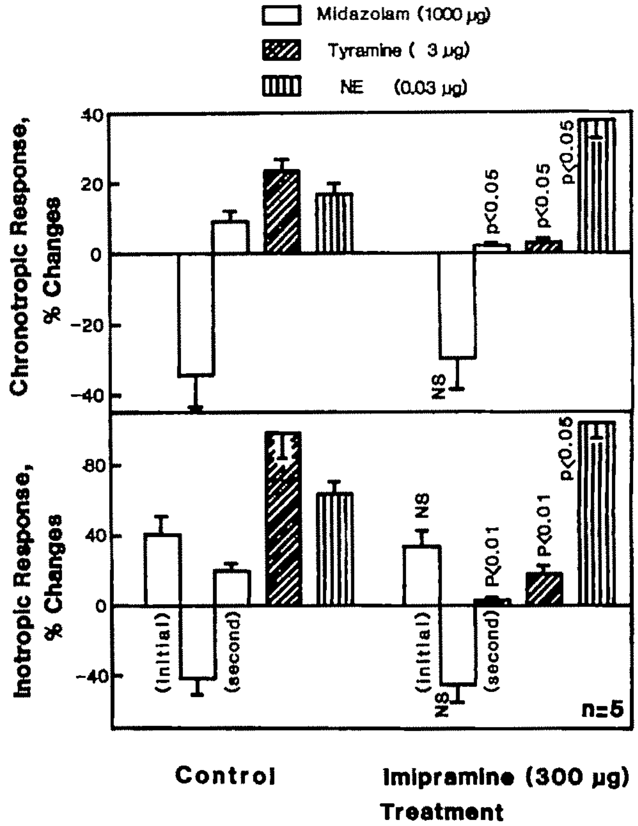

Figure 6. Effects of 300 μg of imipramine on the percentage changes in chronotropic and inotropic responses to 1000 μg of midazolam, 3 μg of tyramine, and 0.03 μg of norepinephrine (NE) in five isolated atria. Vertical lines show SEM. Comparisons are with control values (paired t-test); NS means no statistical significance ($P > 0.05$). Baseline levels of atrial rate and contractile force in the five atria were 103 ± 6 (mean ± SEM) beats/min and 2.9 ± 0.5 g, respectively.

μg NE ($P < 0.05$ and $P < 0.05$, respectively). Tetrodotoxin, a fast inward sodium channel blocker, at a dose of 3 μg significantly suppressed negative followed by positive chronotropic and inotropic responses to 3 μg of nicotine ($P < 0.01$, $P < 0.05$, $P < 0.05$, and $P < 0.01$, respectively). With the same dose, TTX did not modify the cardiac responses to 1000 μg of midazolam in four experiments.

Pharmacologic Basis of Negative Chronotropic and Inotropic Responses to Midazolam

Atropine, a muscarinic antagonist, at a dose of 3 μg significantly inhibited the negative chronotropic and inotropic responses to ACh ($P < 0.01$ and $P < 0.005$,

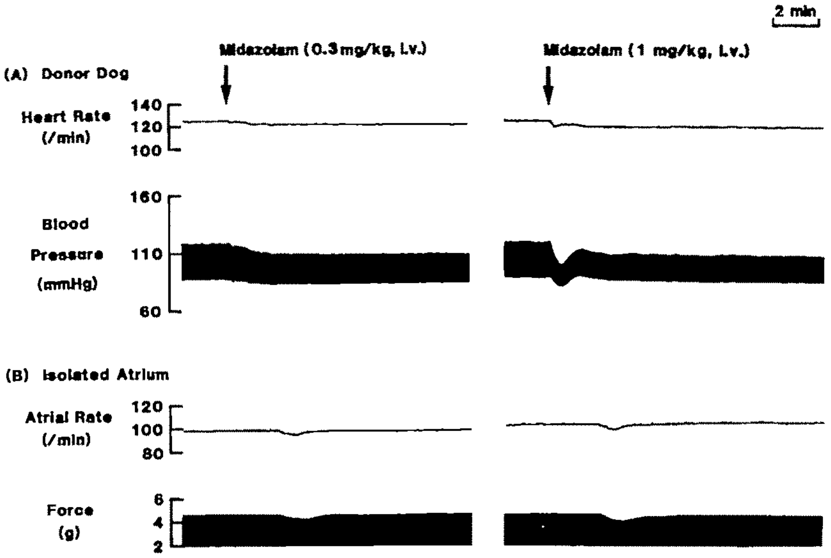

Figure 7. Effects on the heart rate and blood pressure of the intact donor dog (A) and on the atrial rate and contractile force in the isolated canine atrium perfused with donor's blood (B) when 0.3 or 1 mg/kg of midazolam was administered intravenously to an anesthetized donor dog.

respectively), but the negative chronotropic and inotropic responses to midazolam (1000 μg) were not affected in four experiments. Effects of R05-4864, a selective ligand for peripheral benzodiazepine binding sites, on the cardiac responses to midazolam were also examined. R05-4864 (100–1000 μg) alone induced significant negative chronotropic and inotropic effects ($P < 0.05$ and $P < 0.05$, respectively), which were calculated by subtracting solvent-induced, slight negative effects. However, R05-4864 at doses of 100, 300, or 1000 μg had no effect on the cardiac responses to midazolam (3–1000 μg) in three experiments.

Hemodynamic Actions of Intravenous Injections of Midazolam in Donor Dogs

Midazolam was administered intravenously to donor dogs in doses of 0.1–1 mg/kg. Midazolam, 0.1–1 mg/kg IV, decreased heart rate and arterial pressure in the donor dog in a dose-related manner (Fig. 7). In two of five experiments, the change in blood pressure after 1 mg/kg of midazolam included three phases: transient reduction, brief elevation, and, finally, long-lasting (about 90 min) reduction (Fig. 7). The effects on the isolated atrium of perfusion with donor's blood when midazolam was injected intravenously in donor dogs included small negative chronotropic and inotropic responses but never positive ones. The threshold dose in donor dogs for inducing these effects in the isolated atrium preparation was approximately 0.1 mg/kg IV. The effects of midazolam on atrial rate and contractile force appeared ~2.5 min after the end of the intravenous injection, this being the time required for the donor dog blood to reach the atrial preparation. Data summarizing five experiments are shown in Figure 8.

Discussion

In the present study, midazolam injected directly into the sinus node artery had a negative chronotropic effect, as well as a negative inotropic effect similar to that previously observed in the isolated preparation (7). However, the data obtained in the present study also demonstrate that midazolam in increasing doses additionally has positive chronotropic and inotropic properties in the isolated heart.

The negative chronotropic and inotropic and the initial positive inotropic responses to midazolam were not altered by pretreatment with a potent antimuscarinic agent, atropine, or by a potent β-adrenoceptor blocking agent, propranolol, respectively. This indicates that these responses were not mediated by cholinergic or adrenergic mechanisms. Moreover, they were not affected by R05-4864, a compound with high affinity for the peripheral benzodiazepine binding sites (12,13). Thus, we suggest that midazolam has not only a direct depressant effect on the sinoatrial nodal pacemaker activity but also both direct stimulating and depressant effects on the atrial contractility. On the other hand, the positive chronotropic and the secondary positive inotropic responses to high doses of midazolam were markedly reduced by propranolol, indicating that the positive responses were produced by a release of catecholamine from sympathetic nerve terminals in the isolated heart. In this study, the midazolam-induced positive chronotropic and secondary inotropic responses were significantly diminished by

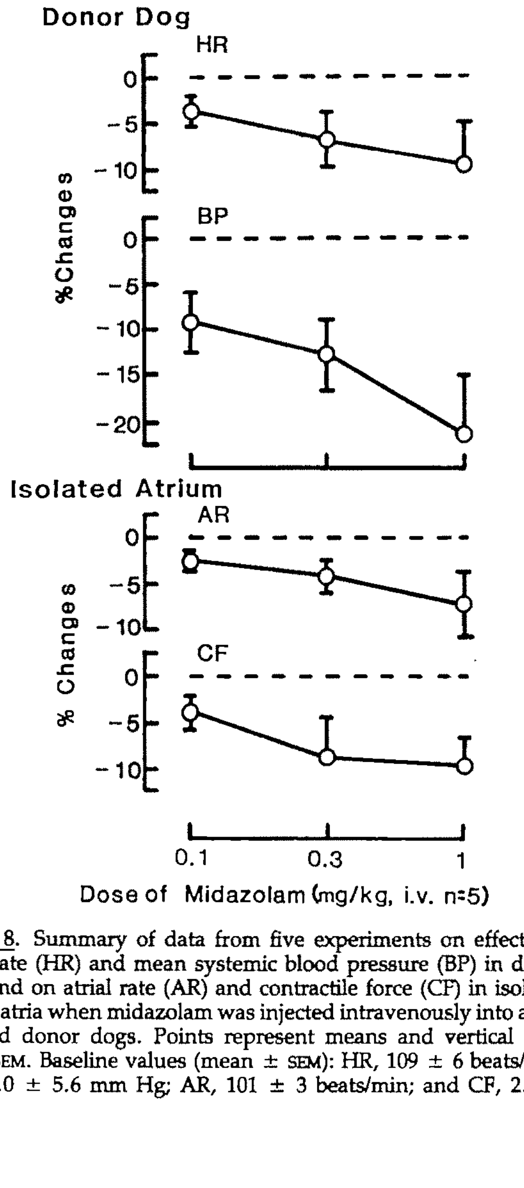

Figure 8. Summary of data from five experiments on effects on heart rate (HR) and mean systemic blood pressure (BP) in donor dogs and on atrial rate (AR) and contractile force (CF) in isolated canine atria when midazolam was injected intravenously into anesthetized donor dogs. Points represent means and vertical lines show SEM. Baseline values (mean ± SEM): HR, 109 ± 6 beats/min; BP, 99.0 ± 5.6 mm Hg; AR, 101 ± 3 beats/min; and CF, 2.6 ± 0.3 g.

treatment with imipramine, which blocks the NE uptake in sympathetic nerve terminals (15). In addition, the responses were not influenced by TTX, which blocks nerve excitation in the autonomic nervous system (16,17). Thus, it is concluded that at high doses midazolam liberates a catecholamine by a tyraminelike action, i.e., neuronal uptake with stoichiometric displacement of norepinephrine.

Recently, we reported that a dissociative anesthetic agent, ketamine, produced indirect cardioexcitatory effects by a tyraminelike action, as well as direct cardioinhibitory effects by which high doses depress atrial contractility rather than pacemaker activity (9). A clinical IV dosage of 1 mg/kg ketamine is known to induce hypertension and tachycardia (18,19). In many clinical and experimental studies, an increase in plasma catecholamine levels after ketamine administration has been reported (20,21). As shown in Figure 3, intraarterial ketamine produced positive chronotropic and inotropic effects even in a small dose of 3 μg, while the threshold dose of intraarterial midazolam for inducing the positive chronotropic and inotropic effects caused by a tyraminelike action was approximately 100 μg (Fig. 2). Therefore, the catecholamine releasing property of midazolam may be much weaker than that of ketamine. With respect to a direct inhibitory effect on the myocardial contractility, intraarterial ketamine at a dose of 1000 μg produced only a negative inotropic effect in the isolated atrium. We presume that the direct depressant effect of ketamine on the atrial contractile force may mask the appearance of a positive inotropic effect mediated via ketamine-induced catecholamine (9). On the other hand, midazolam at the same intraarterial dose of 1000 μg had a positive inotropic effect mediated by a release of catecholamine, despite its weakly tyraminelike action. Thus, we postulate that the direct inhibitory property of midazolam on atrial contractility may also be much weaker than that of ketamine.

In general, characteristic hemodynamic effects of midazolam include hypotension, which is assumed to result mainly from the peripheral vasodilating action of this drug (4–6). Thus, in the present experiments, the intravenous injection of midazolam into an anesthetized donor dog consistently produced a decrease in arterial pressure in doses of 0.1–1 mg/kg. However, we have observed that the change in blood pressure after administration of 1 mg/kg of midazolam occasionally included a two-phased reduction in pressure, i.e., a transient reduction preceded a long-lasting one as shown in Figure 7. In the present study, midazolam-induced hypotension was usually accompanied by bradycardia in the intact dog, and intraarterial midazolam in a small dose of 10 μg in the isolated atrium preparation consistently produced negative chronotropic and inotropic effects. Therefore, it appears that the initial transient depression of systemic blood pressure seen with a large dose is caused both by the peripheral vasodilating property and by cardiac inhibitory properties of midazolam.

In intact animals and in humans, midazolam frequently induces a slight tachycardia, which is considered reflex in origin due to the decrease in mean arterial pressure (4), an increase in Pa_{CO_2} (22), or an increase in venous pooling (23). In contrast, the heart rate after intravenous midazolam decreased progressively in this study. However, this finding is in keeping with a previous observation in patients who were already anesthetized (24). In the present study, the donor dogs were ventilated mechanically with background anesthesia of pentobarbital that could atten-

uate vagal tone and maintain heart rate at higher levels (25,26). Therefore, under the conditions of this study reflex tachycardia may be concealed by both baseline anesthesia and an opposing bradycardic action of midazolam.

In the present cross-circulation experiments, midazolam administered intravenously to the donor dog had no positive chronotropic or inotropic effects on the isolated atrium perfused with donor's blood, whereas intraarterial injection of midazolam in the isolated atrium preparation did have positive chronotropic or inotropic effects. Possible explanations for this discrepancy might involve the difference in arterial blood concentrations of midazolam. Although providing accurate molar concentrations of midazolam in the blood of the sinus node artery is difficult, it is presumed that, when injected intraarterially at a threshold dose of 10 μg, the maximal target concentration of midazolam for inducing the negative chronotropic and inotropic effects in the isolated atrium was about 96–288 μM, calculated from the perfusion flow rate of 3–9 ml/min and the injection rate of 10 μg/4 sec. From the viewpoint of the threshold dose, it appears that this concentration would be derivable from an intravenous dose of 0.1 mg/kg given in the donor dog, which was the intravenous threshold dose for inducing the negative chronotropic and inotropic effects in the isolated atrium preparation. However, the discrepancy cannot be explained by the difference in blood concentration alone, because the initial positive inotropic effect caused by midazolam at the lowest intraarterial dose of 3 μg was not observed even in the highest intravenous dose of 1 mg/kg. Further studies are necessary to explain this discrepancy.

The changes in cardiac function after administration of midazolam in vivo are relatively minor even with the extremely large dose of 10 mg/kg IV (4,8). Gelman et al. (8), who studied the systemic and splanchnic circulatory effects of midazolam in dogs, suggested that maintenance of cardiac output during midazolam (10 mg/kg IV) anesthesia depends on compensatory mechanisms. They proposed that a decrease in cardiac output after the increase in venous capacitance and the decrease in venous return after midazolam injection might initiate sympathetic reflexes leading to an increase in heart rate and mobilization of venous blood with resulting restoration of the circulation. Their hypothesis suggests the possibility that complete β-adrenergic blockade would result in hypotension and decreased cardiac output after midazolam administration. In the present study, pretreatment with a β-adrenergic blocker, propranolol, prolonged the duration of negative responses of both atrial rate and contractile force to relatively large doses of intraarterial midazolam, but did not prolong these responses to small doses (30 μg and below). Therefore, it seems that a release of catecholamines induced by a tyraminelike action of midazolam might not be as significant as reflex-induced changes within the range of clinical dosages (~0.3 mg/kg IV), but it may take part in a restoration of the circulation in the presence of midazolam overdosage.

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Peripheral Neurotoxicity of 2-Chloroprocaine and Bisulfite in the Cat

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FORD DJ, RAJ PP. Peripheral neurotoxicity of 2-chloroprocaine and bisulfite in the cat. Anesth Analg 1987;66:719–22.

The responses of peripheral nerves less than 6 hr after and 2 weeks after exposure to 2-chloroprocaine (2-CP) and bisulfite (BS) were studied in cats using electrophysiologic techniques and by light and electron microscopy. Three percent 2-CP with 0.07% or 0.2% BS was not toxic to peripheral nerves. Three percent 2-CP with 1.2% BS and 1.2% BS (pH 2.8) alone had an acute effect on the peripheral nerves but no chronic effect. Ten percent BS (pH 2.8) caused Wallerian degeneration. However, at pH 4.8, no chronic toxicity was observed. Using conductivity measurements, it was shown that 2-CP and BS, when mixed, form an ion pair in solution that lowers the effective concentration of BS.

Key Words: ANESTHETICS, LOCAL—2-chloroprocaine. TOXICITY—bisulfite, 2-chloroprocaine.

The problem of peripheral nerve toxicity of 2-chloroprocaine (2-CP) has been examined in four different preparations with four different results. Pizzolato and Renegar (1) injected 0.1 ml of 1% 2-CP 3 to 30 times around the sciatic nerve of the rat and concluded that 2-CP was no more toxic than saline. Barsa et al. (2) bathed rabbit vagus nerves in situ in 3% 2-CP and concluded that 2-CP was more toxic than lidocaine or bupivacaine. Gissen et al. (3) exposed rabbit vagus nerves in vitro to 2-CP and bisulfite (BS), both separately and together, and concluded that BS was neurotoxic but 2-CP was not. Finally, Myers et al. (4) and Kalichman et al. (5) injected 1 ml of 2-CP and BS, both separately and together, extrafascicularly but under the mesoneurium of exposed rat sciatic nerves. They concluded that 2-CP, but not BS, caused nerve damage. The above studies suggest that the toxicity of 2-CP and BS is very dependent on the model used to assess the toxicity.

From the clinician's point of view, the four models are not completely satisfactory. Clinically, local anesthetics are injected around nerves into intact tissue. Local anesthetics are not applied to excised nerves or to exposed nerves, or injected under the mesoneurium. The purpose of this study was to examine the toxicity of 2-CP and BS in a model more closely related to the clinical situation.

Methods

Part I

Twenty-eight cats (44 nerves) were used to study the acute effects of 2-CP and BS on the cat saphenous nerve. The cats were cared for by the Department of Laboratory Animal Medicine. On the day of an experiment, each cat was anesthetized with 50 mg/kg ketamine plus 0.1 mg atropine given IM and the appropriate areas shaved. Following 3 mg succinylcholine IM, the cats were intubated and mechanically ventilated. Anesthesia was maintained with 0.1–1% methoxyfluorane, 70% N_2O, and 30% O_2. Next arterial and venous cannulae were placed in the carotid artery and superficial jugular vein. The saphenous nerve was exposed at the groin and then isolated approximately 9 cm distal. Between the two cutdowns, a small incision was made through the skin so that the saphenous nerve could be seen through the subdermal tissue. A pair of stainless-steel stimulating electrodes was placed in contact with the nerve at the groin, and a pair of platinum recording electrodes was hooked under the nerve at the distal site.

A-beta and A-delta fibers were stimulated with a supramaximal rectangular pulse 0.1 ms in duration and about 15 volts in amplitude. C-fibers were stimulated with a supramaximal rectangular pulse 1 ms by 40 volts. The compound action potentials (CAP)

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Table 1. Percent Recovery of Compound Action Potential (av ± SEM)

Solution	pH	N	Fiber type		
			A-β	A-δ	C
Saline	—	9	87 ± 5[a]	84 ± 5	95 ± 7[a]
3% 2-CP + 0.07% BS	4.4	6	88 ± 14	86 ± 10	88 ± 6
3% 2-CP + 0.20% BS	2.8	7	84 ± 9	92 ± 10[a]	97 ± 10[a]
3% 2-CP + 0.60% BS	2.8	6	60 ± 11	67 ± 10	74 ± 7
3% 2-CP + 1.2% BS	2.8	8	64 ± 6	69 ± 4	64 ± 4[b]
0% 2-CP + 1.2% BS	2.8	8	53 ± 14[b]	49 ± 9[b]	72 ± 9

Abbreviations: BS, sodium bisulfite; 2-CP, 2-chloroprocaine.
[a,b] $P < 0.05$.

Table 2. Duration of Block (hrs)

Solution	n	Fiber type (av ± SD)		
		A-β	A-δ	C
1.2% BS	3	4.8 ± 1.1[a]	2.6 ± 1.2	1.2 ± 0.5
1.2% BS + 3% 2-CP	8	2.6 ± 0.9[b]	3.1 ± 0.7	3.5 ± 0.9

Abbreviations: BS, sodium bisulfite; 2-CP, 2-chloroprocaine.
[a,b] $P < 0.005$.

were recorded and amplitudes measured on a recording oscilloscope. The fiber types were identified by their latencies: A-β, 1.5 msec; A-δ, 10 msec; and C-fibers, 100 msec.

One milliliter of one of the test solutions (described in Table 1) was then injected perineurally between the recording and stimulating electrodes. The incision through the skin allowed both the nerve and the needle tip to be visualized. After the injection of the test solution, the amplitudes of the CAPs were measured for the next 6 hr. The onset of block was defined as the interval between the time of injection and the time the CAP disappeared. The duration of block (Table 2) was defined as the interval between the time of injection and the time the CAP returned to 50% of its final value. The percent recovery was determined for each fiber type and injected solution by comparing the preinjection CAP amplitude to the CAP amplitude after 6 hr. The groups were compared using ANOVA and the Kruskal-Wallis critical difference test. The P values are indicated in the tables.

Part II

Two groups of cats were used to study the chronic effects of 2-CP and BS on cat peripheral nerves. Cats in both groups were anesthetized with 50 mg/kg ketamine plus 0.1 mg atropine and the appropriate areas shaved. A small incision was made over the saphenous nerves in the hind legs and over the lateral antebrachial cutaneous nerves in the forelegs. The solutions (1 ml) were injected perineurally as in Part I. The solutions injected in a group of four cats were 1) 1.2% BS; 2) 1.2% BS plus 3% 2-CP; 3) 0.2% BS + 3% 2-CP; and 4) saline ($n = 4$ for each solution). The solutions injected into a group of two cats were 10% BS (pH 2.8) and 10% BS (pH 4.8) ($n = 4$ for each solution). In order to conserve cats, a saline control was not included for this group. Rather the control nerves from the previous group of four cats were used as controls. All four legs of the cats were used and the solutions were rotated to avoid a positional bias (front vs back). The cats were then returned to their cages. Two weeks later, the cats were prepared for the electrophysiologic studies as described in Part I, except that the CAP of the antebrachial cutaneous nerves (front legs) was also measured. The CAPs of the experimentally treated nerves were compared with the CAPs of the saline-treated nerves. After the electrophysiologic measurements, the cats were sacrificed and the tissue fixed in situ by transcardial perfusion with glutaraldehyde-formaldehyde-cacodylate buffer. Sections of all four nerves proximal, distal, and at the injection site were removed and postfixed in OsO_4 and $K_3Fe(CN)_6$. The sections were stained with toluidine blue, mounted in plastic, sectioned for light and electronmicroscopic examination, and examined by a neuropathologist who had no knowledge of the history of the slides (Table 3).

Part III

Conductivity experiments were used to estimate the dissociation constant of BS and 2-CP. Since the bi-

Table 3. Neurotoxicity of 10% Bisulfite

Compound action potentials[a]	Fiber type (av ± SD) A-β	A-δ	C
pH 2.8 (n = 4)	43 ± 28	22 ± 10	35 ± 55
pH 4.8 (n = 4)	129 ± 35	124 ± 34	100 ± 11
	$P < 0.01$	$P < 0.001$	$P < 0.06$
Morphology changes			
pH 2.8 (n = 4)	All showed Wallerian degeneration.		
pH 4.8 (n = 4)	All were normal by light microscopy.		

[a]Values are percent of controls (see Methods).

sulfite salt of 2-CP was not available, it was necessary to mix 2CP-HCl with sodium bisulfite. This resulted in a solution of NaCl and the bisulfite salt of 2-CP. Sodium bisulfite and 2CP-HCl (supplied by Astra Pharmaceutical) were dissolved together to a concentration of 100 mM (pH 4.2). This solution was then diluted with distilled water (adjusted to pH 4.2 with HCl) and the conductivity of each solution determined. The conductivity of NaCl solutions (pH 4.2) from 100 mM to 2 mM was also determined. These conductivities were subtracted from the conductivities of the sodium bisulfite/2CP-HCl solutions to give the BS:2CP conductivities. The experiment was done three times and the average results reported in Table 4. The data were analyzed according to Moore (6) using the following formulas:

$$S = D/C \tag{1}$$

$$K_d = [BS]\,[2CP]/[2CP:BS] \tag{2}$$

$$K_d = S^2C/S_0(S_0 - S) \tag{3}$$

where K_d = dissociation constant, C = concentration of 2CP:BS, D = conductivity of solution of 2CP:BS, S = specific conductivity, and S_0 = specific conductivity of 2CP:BS at infinite dilution.

Table 4. Dissociation Constant (K_d, ML^{-1}) for Bisulfite Salt of 2-CP

Concentration of reactants (M) sodium bisulfite and 2-chloroprocaine	K_d Average	SD
0.1	0.035	0.001
0.04	0.036	0.006
0.02	0.025	0.005
0.01	0.022	0.008
0.004	0.016	0.007
0.002	0.014	0.002

Results

Part I

The acute effects of 3% 2-CP and BS on the cat saphenous nerve are shown in Tables 1 and 2. Low concentrations of BS (0.07% and 0.2%) did not affect the recovery of the nerves. Higher concentrations (0.6% and 1.2%) caused incomplete recovery over the 6 hr of the experiment (Table 1). The presence of 3% 2-CP did not adversely affect the recovery of nerves exposed to 1.2% BS (last two groups). All solutions containing 3% 2-CP blocked the nerves for about the same length of time: A-β, 2.7 hr; A-δ, 3.4 hr; and C-fibers, 3.6 hr. The onset of all the blocks was rapid—less than 5 mins.

One milliliter of 1.2% BS, pH 2.8, produced the following results. Four nerves were incompletely blocked and all four recovered; four nerves were completely blocked, three nerves recovered, and one nerve did not recover. Table 2 shows the duration of block for the three nerves that were completely blocked and recovered. For comparison, the duration of nerve block for 3% 2-CP containing 1.2% BS (pH 2.8) is included. The onset of the blocks was slower with 1.2% BS than with 3% 2-CP. For the four nerves that were blocked completely with 1.2% BS, the onset of the A-β fibers was 44 mins; A-δ fibers, 12 mins; and C-fibers, 5 mins.

Part II

Saline, 3% 2-CP plus 0.2% BS and 3% 2-CP plus 1.2% BS, caused no damage detectable by recording compound action potentials and light and electronmicroscopy after 2 weeks. One of four nerves injected with 1.2% BS did not conduct impulses and showed severe Wallerian degeneration both proximal and distal to the injection site.

When 10% BS, pH 4.8, was injected near the nerves,

Table 5. Percent Concentration of Free Bisulfite[a]

(2-CP)	$(BS)_{total}$	$(BS)_{free}$
3	1.2	0.55
3	0.6	0.20
3	0.2	0.053
3	0.07	0.017

[a]Calculated using K_d = 0.03 ml^{-1}.

no damage was detected at 2 weeks. However, 10% BS, pH 2.8, caused a decrease in the CAP amplitudes of all three fiber types and caused Wallerian degeneration (Table 3). The CAP of the three fiber types were depressed about equally. Light and electron-microscopy examination also indicated that the different fiber types were damaged about equally.

Part III

The dissociation constant for BS and 2-CP varied with the concentration of the reactants (Table 4). At high concentrations (100 mM to 40 mM), K_d was 35 ± 4 (mM/L) (n = 6). At low concentration (20 mM to 2 mM), K_d was 20 ± 7 (n = 10). In Table 5 the concentration of free BS is shown at different concentrations of reactants.

Discussion

The problem of 2-CP/BS toxicity has now been examined in five different peripheral nerve models. The results at this study are consistent with, or at least do not contradict, the previous studies. In addition, this study helps clarify certain concepts of 2-CP/BS toxicity.

First, in the in vivo models, concentrations of BS equal to or less than 0.2% caused no damage. Only when the concentration of BS was increased to 10% (pH 2.8), as in this study, was permanent damage induced. The toxicity of very low concentrations of BS reported for an in vitro model suggests that the buffering and diluting effects of the tissue and local circulation are important protective mechanisms against BS toxicity.

Second, the mechanism proposed by Gissen et al. (3) to account for the toxicity of BS is supported by this study. Gissen et al. proposed that SO_2 diffuses intracellularly and rehydrates, forming the strong acid H_2SO_3 (analogous to CO_2 and H_2CO_3). The large myelinated A-β fibers would be protected from the SO_2 by their myelin sheath. Therefore, the onset of the block of the A-β fibers by BS would be delayed relative to the C-fibers. However, once the SO_2 had penetrated the nerve and lowered the intracellular pH, the myelin sheath would prevent the SO_2 from diffusing out. This accounts for the prolonged block of the A-β fibers relative to the C-fibers. Also consistent with this mechanism is our finding that 10% BS at pH 4.8 was not neurotoxic, whereas at pH 2.8 it was.

Third, in the in vivo models used by Barsa et al. and Myers et al., 2-CP was shown to be toxic. In their models, the exposure time of the 2-CP to the nerve was longer than in either Pizzolato's or this study. The extended time of exposure may have contributed to the toxicity of 2-CP.

An unexpected result of this study was evidence that 2-CP and BS form an uncharged complex in solution. Because in this peripheral nerve model the BS is the toxic chemical in the local anesthetic preparation, lowering the concentration of free BS would reduce the toxicity of the preparation. The consequences of this interaction were observable in this study at high concentrations of BS. However, other investigators have not observed an ameliorating effect of 2-CP on low concentrations of BS (0.2%). The clinical significance of this interaction is open to speculation.

One of the nerves exposed to 1.2% BS showed Wallerian degeneration both proximal and distal to the injection site after 2 weeks. We do not have an explanation for this result, but argue that it is not related to the perineural injection of the BS for the following reasons. First, the other three nerves exposed to 1.2% BS were normal after 2 weeks. Second, 10% BS caused less damage. Third, 10% BS caused damage only at the injection site or distally, not proximally. A possibility is that the nerve was damaged by the needle and the BS gained access to the nerve through the damaged sheath.

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Histamine Release by Four Narcotics:
A Double-Blind Study in Humans

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Histamine release and hemodynamic changes associated with four narcotics were studied in 60 adults (28 men, 32 women) scheduled for general surgery under balanced anesthesia. Under double-blind conditions, incremental equipotent doses of meperidine, morphine, fentanyl, or sufentanil were administered IV for induction of anesthesia, prior to thiopental, succinylcholine, and intubation. Arterial blood samples were drawn before and 1, 6, and 20 min after narcotic administration. Of the 16 patients given meperidine (mean dose 4.3 ± 0.2 (SEM) mg/kg), five (31%) had clinical signs (hypotension, tachycardia, erythema) and elevations in plasma histamine levels ranging from 3.2 to 49.7 ng/ml 1 min after narcotic administration. Plasma epinephrine levels at this time were also elevated in these five patients. One of the ten patients given morphine (0.6 ± 0.02 mg/kg) developed hypotension, tachycardia, and an increase in plasma histamine level to 12.4 ng/ml. None of 34 patients given either fentanyl (7 ± 0.4 μg/kg) or sufentanil (1.3 ± 0.1 μg/kg) had clinical signs of histamine release or elevations of plasma histamine levels. In the six patients in whom histamine release occurred, there was a significant correlation between the histamine levels at 1 min and the magnitude of change in heart rate, blood pressure, and plasma epinephrine level. All six histamine releasers were young women, ranging in age from 18 to 35 yr. Histamine release occurred more frequently after meperidine than after the other narcotics, including morphine, and the degree of hemodynamic compromise was related to the increase in plasma histamine concentration.

Key Words: HISTAMINE, RELEASE—narcotics. ANESTHESIA, INTRAVENOUS—narcotics. ANALGESICS—morphine, meperidine, fentanyl, sufentanil.

Narcotic analgesics, as well as other drugs and colloid solutions commonly used during the perianesthetic period, are capable of releasing histamine both in vitro (1,2) and in vivo in animals (3–5) as well as in humans (6–10). This histamine release is thought not to represent a true allergic response, that is, an IgE antibody-mediated reaction, but rather the ability of these basic drugs to act directly, in some unknown manner, upon the blood and tissue cells to release histamine (1,11–13), the so-called "pseudo-allergic" or "anaphylactoid" reaction (11,14–16). Such reactions have been estimated to occur as frequently as one in every 400–1000 anesthetics (17,18).

Recently Rosow et al. (10,19) reported elevated plasma histamine levels accompanied by hemodynamic and cutaneous changes after administration of large doses of IV morphine to patients scheduled for cardiac surgery. However, equipotent doses of fentanyl did not cause elevations of plasma histamine or hypotension. Because the in vivo release of histamine by opioids, muscle relaxants, and other compounds is dose dependent (8,10,13,19), and because the amount of a drug required correlates inversely with potency, we decided to study the propensity to release histamine of four narcotic analgesics differing greatly in potency. The drugs were given in a double-blinded manner for induction of balanced anesthesia.

Methods

This study was approved by the UCLA Human Subjects' Protection Committee. As previously reported (20), 60 ASA Class I and II patients between the ages of 18 and 65, without a history of cardiovascular disease, sensitivity to opioids, or other drug allergy, and scheduled to undergo general, orthopedic, or gynecologic surgery, were identified on the day before operation. Written informed consent was obtained,

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Table 1. Patient Data

Drug	n	Sex male/female	Age (yr)	Weight (kg)	Mean blood pressure (mm/Hg)	Heart rate (beats/min)	Plasma catecholamines (pg/ml) NE	EPI
Sufentanil	17	8/9	43 ± 3	66 ± 4	89 ± 3	77 ± 4	130 ± 17	50 ± 9
Fentanyl	17	11/6	40 ± 4	68 ± 4	89 ± 2	77 ± 3	185 ± 18	41 ± 6
Morphine	10	3/7	37 ± 3	72 ± 6	89 ± 5	79 ± 3	164 ± 35	23 ± 4
Meperidine	16	6/10	40 ± 4	71 ± 3	88 ± 3	75 ± 3	174 ± 15	79 ± 28

Values given are mean ± SEM values for patients' ages, weights, hemodynamics, and plasma catecholamine values immediately before induction of anesthesia with narcotics. There are no significant intergroup differences ($P < 0.05$).

and the patients were assigned randomly (by computer-generated random numbers) to receive one of four narcotic agents, as part of their anesthetic management.

Study Protocol

All patients were premedicated with diazepam, 5–10 mg, and droperidol, 0.5 mg, given orally and intramuscularly (respectively) 60 min before coming to the operating suite. Alternatively, both drugs were given intravenously in the preoperative room, approximately 25 min before induction of anesthesia. After arrival in the operating room, IV and radial artery catheters were placed under local anesthesia. ECG electrodes were attached, and baseline measurements were made. The narcotics were supplied in 10-ml syringes labeled "Narcotic. Equivalent to 33.3 mg/ml meperidine." The syringes contained meperidine 33.3 mg/ml, morphine 4 mg/ml, fentanyl 50 μg/ml, or sufentanil 10 μg/ml. These drug concentrations were based upon relative potencies reported in the literature (21–24). Neither the patients, their anesthesiologists, nor the investigators knew which of the four opioids was used.

After 3 min of breathing 100% oxygen by face mask, and precurarization with 1 mg of pancuronium IV, the patient received the blinded narcotic drug IV over 10 min or less, in 1- to 2-ml increments, up to a maximum amount of 0.15 ml/kg. If the patient became unresponsive with a lesser dose, or if side effects such as severe flushing/hives, clinically significant hypotension, changes in heart rate, or truncal rigidity occurred, the remainder of the anticipated loading dose was not given. To assess the state of consciousness during administration of the opioid, the anesthesiologist quietly but firmly instructed the patient to breathe, open his or her eyes, and/or to follow other commands. Respiration was manually assisted if necessary. After narcotic administration was complete, the patient was given thiopental, 1–4 mg/kg IV, followed by 1 mg/kg succinylcholine, and the trachea was intubated. After intubation, patients were ventilated with 60–67% nitrous oxide in oxygen to maintain normal arterial blood gas tensions. No further muscle relaxants were given, nor did surgery commence, before the end of the study observation period.

Electrocardiogram, intraarterial blood pressure, and heart rate were recorded continuously (Hewlett-Packard direct-writing polygraph) from before induction until the end of the study period. The skin was observed for evidence of erythema and/or edema. Arterial blood samples for determination of the concentrations of plasma histamine and catecholamines were drawn immediately before the narcotics were given, after the end of narcotic administration, i.e., before thiopental or succinylcholine (1 min), and immediately after intubation (6 min). Approximately 20 min after the end of narcotic administration, another arterial sample was obtained, but was assayed for histamine only if elevations were found in either of the previous two samples.

Plasma histamine levels were determined by the radioenzymatic method of Beaven et al. (25) as modified by Moss et al. (8). In this method, histamine is converted to N-methyl-histamine using a partially purified preparation of rat kidney histamine-N-methyltransferase. The methyl donor is tritium labeled S-adenosyl-methionine (New England Nuclear Corp.). Labeled N-methyl-histamine is purified by extraction and thin-layer chromatography. Samples were measured in duplicate, and spiked duplicates were run to quantitate the conversion. Our laboratory baseline values for plasma histamine measured by this method, as established in plasma from arterial blood drawn from 14 normal "volunteer" coworkers, ranged from 0.04 to 0.33 ng/ml, with a mean value of 0.19 ± 0.02 (SEM). These baseline levels are somewhat lower than those reported by Moss et al. (8,19,26), but are similar to the levels found by Beaven et al. (25), and by Dyer et al. (27) using the same method, and by Lorenz and Doenicke (28), who used a fluorometric assay.

Table 2. Induction Doses

Drug	Concentration per ml	Induction dose/kg Calculated	Induction dose/kg Actual	Dose thiopental (mg/kg)
Sufentanil	10 μg	1.5 μg	1.3 ± 0.1 μg	3 ± 0.4
Fentanyl	50 μg	7.5 μg	7.0 ± 0.4 μg	3 ± 0.5
Morphine	4 mg	0.6 mg	0.6 ± 0.02 mg	3 ± 0.6
Meperidine	33.3 mg	5.0 mg	4.3 ± 0.2 mg	4 ± 0.7

Concentrations of the blinded drugs, and mean ± SEM values for induction doses. There were no significant intergroup differences in the dose of thiopental given ($P < 0.05$).

Table 3. Plasma Histamine Levels in Patients Given Sufentanil or Fentanyl

		Plasma histamine levels (ng/ml)		
			Time after narcotic	
Drug	n	Baseline	1.2 ± 0.1 min	5.8 ± 0.5 min
Sufentanil	17	0.13 ± 0.01	0.23 ± 0.06	0.18 ± 0.03
Fentanyl	17	0.12 ± 0.01	0.14 ± 0.01	0.15 ± 0.01

Mean ± SEM plasma histamine levels before and after narcotic administration in patients given fentanyl or sufentanil. There were no significant changes from baseline levels ($P < 0.05$).

Plasma norepinephrine and epinephrine levels were measured by a previously reported (29) and verified (30) high-performance liquid-chromatography method.

In the statistical treatment of demographic, hemodynamic, catecholamine, and histamine data, intergroup differences were tested first by one-way analysis of variance. When statistical significance was demonstrated, individual group differences were isolated using a weighted t-test, in which the critical probability for significance (P) was calculated as P divided by the number of drug groups. Thus, to achieve significance at the 5% level, P had to be less than $P/4$ or less than 0.0125. Intragroup differences were compared by analysis of variance for repeated measure, with Bonferroni's modified t-test used to isolate further significant differences. Linear regression analysis and correlation coefficients were calculated between hemodynamic and catecholamine values and plasma histamine levels. Correlation coefficients (r) with corresponding $P < 0.05$ were considered statistically significant.

Results

Baseline plasma histamine levels prior to narcotic administration in the 60 premedicated patients in the present study ranged from 0.06 to 0.35 ng/ml, with a mean value of 0.13 ± 0.01. In accordance with the literature (7,12,14,31), histamine levels of 1.5 ng/ml or greater are considered abnormal in this investigation.

Patient demographics and baseline hemodynamic values and plasma catecholamine levels have been reported previously (20,32) and are given in Table 1. There were no significant intergroup differences. Table 2 shows the calculated, or intended, induction dose of the four blinded narcotics, the actual dose given, and the dose of thiopental. Half the patients given meperidine did not tolerate the full induction dose (Table 2). Four of these patients developed unacceptable hypotension, and five had severe tachycardia, accompanied in three cases by marked flushing of the visible skin areas. One of the ten patients given morphine also became erythematous, hypotensive, and had an increase in heart rate; however, this patient, as well as all of the others given morphine, received the full calculated induction dose. With fentanyl and sufentanil, no patient developed erythema, hypotension, or tachycardia, but several did not receive the full induction dose of narcotic for other reasons (unconsciousness, rigidity). The mean dose of thiopental was the same for all four groups.

Plasma histamine levels in patients given fentanyl or sufentanil are shown in Table 3, as well as the mean time after the end of narcotic administration at which the blood samples were taken. No abnormally elevated plasma histamine levels were encountered, and the mean histamine value after either narcotic did not increase significantly above baseline levels.

In Table 4 the plasma histamine levels in the 26 patients given either meperidine or morphine and the sampling times are shown. In this table, patients are subdivided into those who responded with abnormal histamine release (i.e., developed plasma histamine

Table 4. Plasma Histamine Levels in Patients Given Morphine or Meperidine

Drug	n	Baseline		Plasma histamine levels (ng/ml) Time after narcotic 1.2 ± 0.2 min	6.0 ± 0.5 min	23.3 ± 1.8 min
Morphine	10	0.11 ± 0.01	Responder (1)	12.4	0.55	0.15
			Nonresponders (9)	0.31 ± 0.07*	0.27 ± 0.03*	—
Meperidine	16	0.12 ± 0.01	Responders (5)	22.4 ± 9.1*	7 ± 3.3	0.28 ± 0.1
			Nonresponders (11)	0.33 ± 0.07*	0.27 ± 0.05*	—

Mean ± SEM plasma histamine levels before and after narcotic administration in patients given morphine or meperidine. Patients were classified as "responders" if plasma histamine levels increased to >1.5 ng/ml. The six responders included one patient given morphine and five patients given meperidine. Among nonresponders, there were also significant increases in plasma histamine concentrations after the narcotics were given, but these did not approach levels associated with significant clinical effects.
*$P < 0.05$ compared with their paired baseline values.

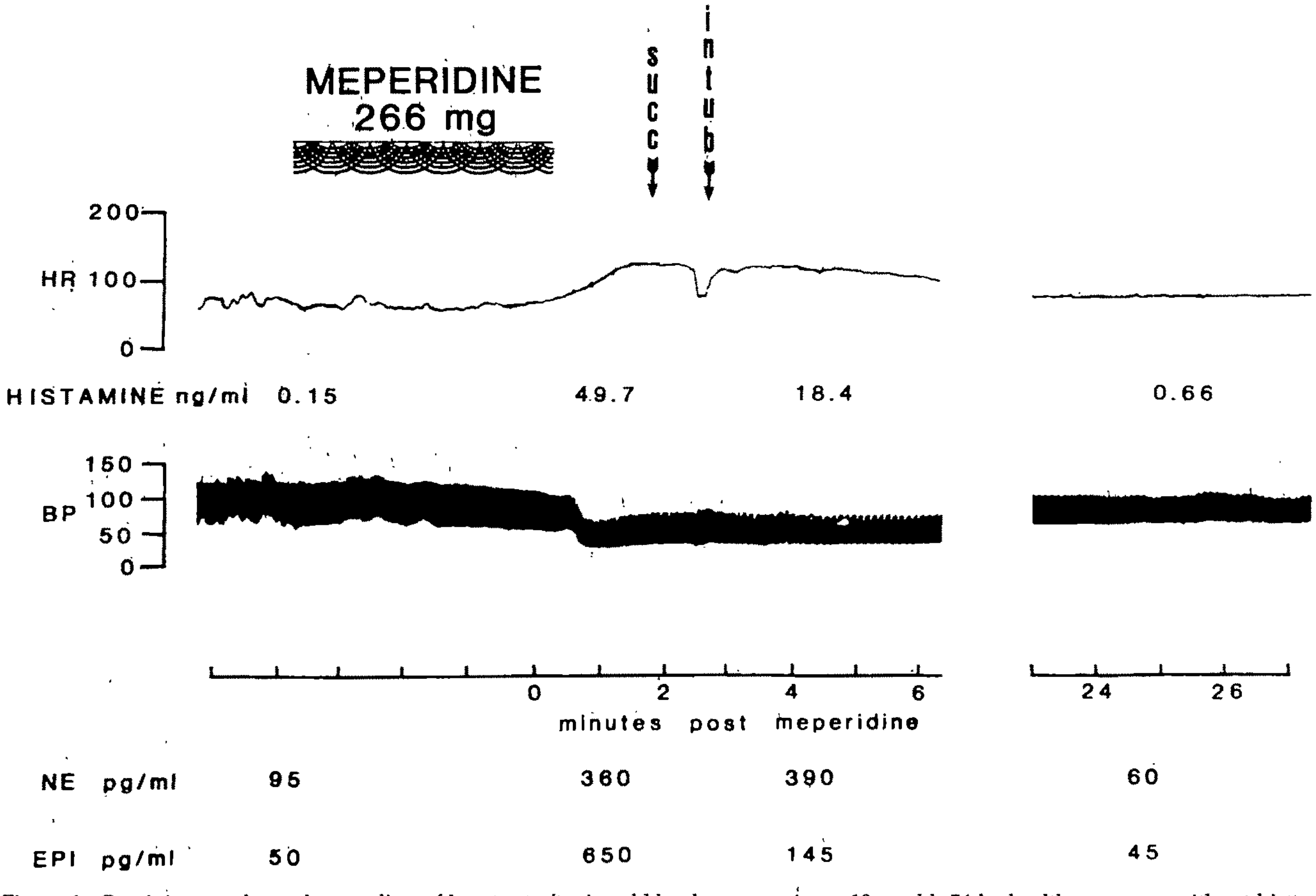

Figure 1. Continuous polygraph recording of heart rate (top) and blood pressure in an 18-yr-old, 54-kg healthy woman, without history of drug allergy, given 4.9 mg/kg meperidine over 4 min. Plasma histamine, norepinephrine (NE), and epinephrine (EPI) levels before and 1, 4, and 24 min after the narcotic are also shown. The administration of meperidine caused a prompt and profound decrease in blood pressure from a baseline value of 130/70 mm Hg to 70/35 mm Hg, accompanied by an increase in heart rate from 72 to 125 beats/min, and a >300-fold increase in plasma histamine concentration. Catecholamine values also increased significantly. Concomitantly the patient turned beet red. Rapid infusion of intravenous fluid and the stimulus of intubation did little to alleviate the situation, nor did administration of 100 μg of intravenous phenylephrine (given at 5 min after the meperidine). By 24 min, hemodynamic function and plasma histamine levels had returned to normal, but not to baseline values; catecholamine levels were again at baseline.

levels > 1.5 ng/ml) and those who did not. As shown, five patients receiving meperidine (31% of the group), and one patient given morphine (10%), had abnormally elevated plasma histamine levels. All six of these patients were female between 18 and 35 yr of age. However, there was no correlation between age and magnitude of plasma histamine levels. In these six patients, the 1-min plasma histamine values ranged from 3.2 to 49.7 ng/ml. The mean value for the five patients who had received meperidine was 22.4 ng/ml,

and the patient given morphine had a plasma histamine level of 12.4 ng/ml. Six minutes after the end of narcotic administration, three patients still had markedly elevated histamine levels, with the mean value for the meperidine group as shown in Table 4. By 20 min after the narcotic all histamine levels were within the normal range.

In the 20 patients (11 meperidine, nine morphine) who did not develop abnormally elevated histamine levels, postnarcotic levels were nevertheless statistically significantly higher than baseline values (Table 4). However, the histamine levels after narcotics in these 20 patients were still within the normal range and were not accompanied by cutaneous or physiologic changes.

Hypotension and tachycardia occurred in all six patients who had abnormally elevated histamine levels after meperidine or morphine. These hemodynamic changes were accompanied by increases in plasma levels of norepinephrine and epinephrine in all but one patient (who received meperidine). An example of this is seen in Fig. 1, which shows the strip chart recording of blood pressure and heart rate and the plasma levels from the patient who had the most severe histamine release. In this patient, who was, at age 18, the youngest of the 60 patients studied, the extreme elevation of plasma histamine to nearly 50 ng/ml was accompanied by profound hypotension, marked tachycardia, and cutaneous erythema. Mean arterial pressure, heart rate, and plasma levels of histamine at 1 min are shown for all six patients in Fig. 2. There was a significant correlation between the plasma histamine concentrations and the changes from baseline values of blood pressure, heart rate, and plasma epinephrine. There was, however, no significant correlation between histamine levels and increases in plasma norepinephrine levels. Although variations in heart rate and blood pressure also occurred in nonresponders who had received meperidine or morphine, these showed no correlation with the slight increases in plasma histamine.

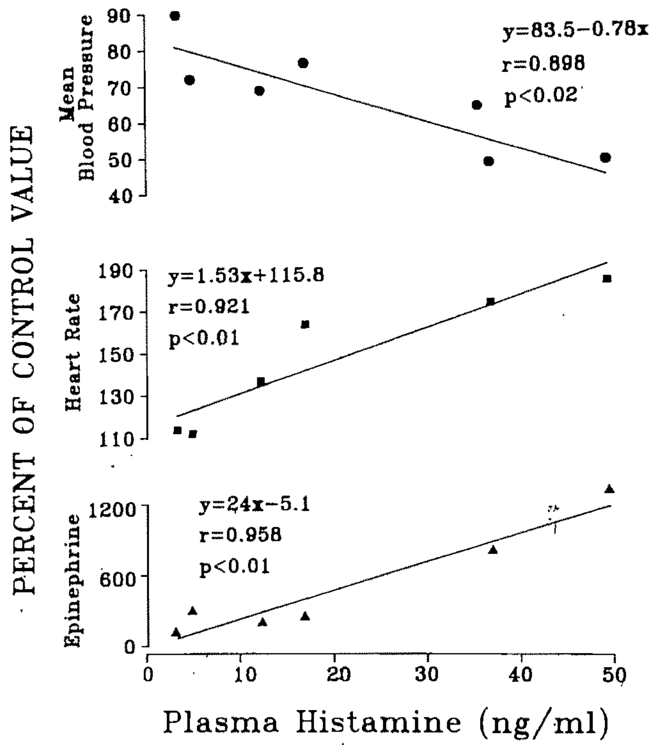

Figure 2. In the six patients who responded with histamine release, regression lines are shown for the relationship between the absolute level of plasma histamine 1 min after narcotic administration and changes (in percent of the prenarcotic control value) in mean arterial blood pressure, heart rate, and plasma epinephrine level. As seen, the correlation was significant for all three parameters.

Discussion

The most important new finding in the present investigation is the fact that in a study during which four narcotics were given intravenously under blinded conditions in equipotent doses and at comparable rates, meperidine (4.3 mg/kg) caused the highest incidence (31%) of histamine release and the highest plasma levels (up to 50 ng/ml) of histamine. Of the ten patients receiving 0.6 mg/kg morphine at a rate of 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$ only one experienced histamine release, and the maximal plasma level in this patient was 12 ng/ml. None of the 34 patients who received fentanyl or sufentanil released histamine, a finding that confirms the results of Rosow et al. (10,26) who used much larger doses of these two agents.

How do our observations fit in with the reported results of others, and especially, should meperidine or morphine be considered the more important releaser of histamine? Although there are no other studies comparing the two drugs directly, there are several reports concerning the incidence and magnitude of histamine release after morphine from the group at the Massachusetts General Hospital (10,19,26,33). These investigators found that plasma histamine levels increased to abnormal levels in all but one of eight patients given 1 mg/kg morphine IV at a rate of 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (10). However, a smaller dose of 0.5 mg/kg of morphine (similar to our dose of 0.6 mg/kg) elicited no increase in plasma histamine, although cutaneous signs (itching, redness, heat, urticaria) were seen (33). The highest plasma histamine value after 1 mg/kg morphine was 20 ng/ml, and only two patients had levels above 10 ng/ml. In contrast, three of our six patients who released histamine after meper-

idine had plasma levels above 15 ng/ml, and the highest value was 50 ng/ml.

Thus, it appears that both morphine and meperidine can elicit histamine release when given intravenously at clinically used doses and rates. The importance of these factors is obvious in the study by Hsu et al. (34) who gave 0.5 or 1.0 mg/kg of morphine as intraarterial bolus injections to patients on cardiopulmonary bypass. This high "rate of administration" caused a rapid massive decrease in systemic vascular resistance, of equal magnitude with both doses, in all patients. Unfortunately plasma histamine levels were not measured.

The present report is the first direct documentation of plasma histamine elevation after meperidine in humans. However, there has been considerable concern about the hypotensive effect of intravenous meperidine ever since the introduction of this synthetic drug (3,35–37), and histamine release, which had been shown to occur in dogs (5), had been suspected but not proven in humans (38).

A relationship between dose and/or administration rate and histamine release in the reports discussed above is suggested but not clear-cut. Clear-cut dose–response curves for histamine release have been reported only for in vitro preparations (1,39–41). Paton (13) characterized the release of histamine after intravascular injections as "explosive." This points toward a steep dose–response relationship that may appear as "all or none." Thus extreme doses would be expected to elicit some histamine release in all subjects (e.g., when Hsu et al. (34) gave morphine in the form of an intraarterial bolus), and lower doses or rates of administration would release little or no histamine. A medium dose of a releasing agent might, even at the same rate of administration, cause widely different responses in different persons. In practical terms, some patients show no histamine release or so little that they are indeed "nonresponders," whereas others given the same dose respond massively.

Since the earliest observations concerning histamine release by drugs, it has been intimated that the total dose or concentration of a drug within a series of chemically related compounds might be related to the number of histamine molecules released (13). This fits in with the present observations and those reported by others in which histamine releasing activity varied roughly inversely to the analgesic potency, or the number of drug molecules administered: meperidine > morphine ≫ fentanyl > sufentanil. Such a hypothesis makes sense if the mechanism of release is one of displacement of histamine from tissue binding sites, as has been speculated (13). However, this hypothesis has been contradicted by Hermens et al. (1), who exposed in vitro human foreskin preparations rich in mast cells to the same molar concentrations of morphine, oxymorphone, and fentanyl, but saw histamine release only with morphine.

The question of the actual relationship between histamine release and hemodynamic changes has been the subject of some discussion (42). Hypotension after high doses of a potent narcotic may also occur, of course, as a result of decreased central sympathetic outflow in patients who have high central tone initially (43). The hallmark of this type of hypotension is that blood pressure and heart rate decrease in parallel secondary to a "resetting of the vasomotor center." On the other hand, hypotension caused by direct peripheral vasodilation (i.e., by histamine) leads to reflex tachycardia.

Our observations (Figs. 1 and 2) are consistent with a causative relationship, both temporal and quantitative; the same conclusion has been drawn by others (5,10,14,15,19,28,31,44). Philbin et al. (19) showed that pretreatment with antagonists to histamine-1 and histamine-2 receptors, together but not singly, markedly attenuated the decrease in systemic vascular resistance after morphine, without affecting the histamine release itself. One noteworthy difference between our observations and theirs is that all of their patients, who were scheduled for cardiac bypass surgery, were receiving propranolol medication. This explains the low initial heart rates, as well as the lack of tachycardia after morphine administration, which they observed in all groups, pretreated with histamine antagonists or not. In contrast, in our patients, hypotension, tachycardia, and epinephrine levels correlated with plasma histamine concentrations (Fig. 2). The question arises whether the tachycardia was due to the histamine itself, or to circulating epinephrine, or was merely an autonomically mediated reflex response to the fall in blood pressure. While it is well established that histamine has a direct positive chronotropic effect in many species including humans, the concentrations required to produce this effect are about two orders of magnitude greater than those seen by us (45). It is possible, therefore, that only the hypotension was histamine induced, whereas the tachycardia was mediated by the baroreceptor reflex, or by epinephrine increase, or both. Even if histamine is a major mediator of cardiovascular changes, this does not preclude the possibility that other endogenous substances are coreleased and may contribute to the symptoms.

Although only hypotension and tachycardia after histamine release were seen in this limited series of relatively healthy patients, other serious effects of histamine have been well documented. These include

depression of AV conduction (45,46), increased cardiac automaticity (47), and other serious cardiac dysrhythmias (48). In addition, Ginsburg et al. have shown that histamine can provoke coronary vasospasm (49).

It is of interest that all histamine releasers in the present investigation were young women. This was so although the sex distribution of the entire study group was even. The preponderance of anaphylactoid reactions in female patients has been noted previously (17,18), and the three published case reports of hypersensitivity to meperidine all concern female patients (35,36,50).

In summary, in a double-blind clinical study of four narcotics, given intravenously as induction agents for balanced general anesthesia, we have found that the incidence of histamine release sufficient to result in abnormal plasma histamine levels was 31% with meperidine, 10% with morphine, and zero with fentanyl or sufentanil. The elevated plasma histamine levels all occurred in young females, and were accompanied by hypotension, tachycardia, and elevation of plasma epinephrine levels.

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Effect of Thoracic Epidural Bupivacaine on Somatosensory Evoked Potentials after Dermatomal Stimulation

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The effect of epidural bupivacaine (9 ml 0.5%) analgesia on early (< 500 msec) somatosensory evoked potentials (SEPs) with electrical stimulation of the T-10 and L-1 dermatomes was examined in eight patients. Cortical amplitudes decreased only insignificantly after stimulation of both dermatomes, despite the presence of sensory analgesia (pin prick) from T-3.5 ± 0.4 to L-2.9 ± 0.4 (mean ± SEM). Latency of the SEP components remained unchanged and sensory threshold increased only insignificantly during blockade. We conclude that thoracic epidural analgesia with conventional doses of bupivacaine provides only a limited blockade of fast conducting afferent nerve fibers.

Key Words: ANESTHETIC TECHNIQUES—epidural; BRAIN—evoked potentials.

Epidural administration of local anesthetics is well-established as a method for providing operative anesthesia and postoperative analgesia. Lumbar epidural analgesia gives excellent pain relief after lower abdominal surgery and orthopedic surgery on lower extremities, whereas for upper abdominal surgery, segmental analgesia may be achieved using a thoracic epidural blockade. Comparison of the degree of afferent neural blockade after lumbar and thoracic epidural injection of local anesthetics has not been directly assessed, but studies of endocrine and metabolic responses to surgery and their modification by epidural analgesia indirectly suggest a reduced afferent blockade during thoracic epidural analgesia (1,2).

In a previous study giving a lumbar (L2–3) epidural blockade with 26.9 ± 1.5 ml 0.5% bupivacaine and a mean dermatomal level of analgesia to T-6.8, somatosensory evoked potentials (SEPs) were found to be significantly reduced (3). The most pronounced decrease in amplitude and increase in latency of SEP was seen at the L-1 dermatome, with a less pronounced reduction in SEP at the T-10 dermatome despite sensory analgesia above this level (3). This discrepancy in afferent blockade might be explained by a higher concentration of the local anesthetic agent in the lumbar area during lumbar epidural analgesia.

The aim of the present study was to determine if thoracic epidural blockade induced at the T-10 level was associated with changes in cortical SEPs after cutaneous electrical stimulation at T-10 and L-1 dermatomes.

Material

Eight patients, four women and four men, mean age 37 yr (range 20–46 yr) were studied. All were scheduled for elective upper abdominal surgery (cholecystectomy) that justified use of a thoracic epidural catheter for management of postoperative pain. None had symptoms, signs, or a history of neuromuscular disease. The patients volunteered for the study and the declaration of Helsinki was respected and informed consent obtained.

Thoracic Epidural Analgesia

A thoracic (T9–10) epidural catheter was inserted by a lateral approach technique and 9 ml of plain 0.5% bupivacaine was injected. SEP recordings were performed before insertion of the catheter and when maximal spread of analgesia (bilateral pin prick) was achieved (35 ± 5 min, mean ± SEM). All recordings were performed before induction of general anesthesia and surgery.

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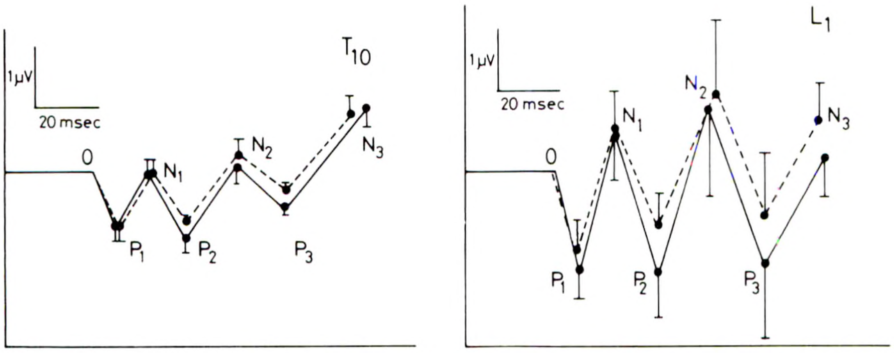

Figure 1. Mean cortical somatosensory evoked potentials before and during thoracic epidural blockade with 9 ml bupivacaine 0.5% after stimulation of the T-10 (left) and L-1 (right) dermatomes before (——) and during (----) blockade. n = 8 (mean ± SEM). Changes in latency not shown.

Stimulation

The sensory nerves of the L-1 and T-10 dermatomes were stimulated at the anterior superior iliac spine and at the midline just inferior to the umbilicus, respectively. The two areas were stimulated at random using a stimulation procedure previously described in detail (3) with an intensity of four times the sensory threshold (ST). ST was defined as the midpoint between the stimulus intensity needed for barely detectable perception of stimulation by the subject and for barely detectable loss of perception of stimulation. Stimulation of muscles was avoided. Stimulation was done before and during the thoracic epidural analgesia with identical stimulation intensity.

Recording

Cortical activity was recorded using platinum needle electrodes (Dantec/DISA 25 C 04, Copenhagen, Denmark) at the midline of the scalp, 2 cm posterior and 5 cm anterior (reference) to vertex C-2 of the International 10–20 system for recording. During each stimulation procedure, 1000 responses were averaged. A Dantec/DISA Neuromatic 2000 neuromyograph was used for stimulation and recording. The amplifier had a bandpass (−3 dB) of 0.5–1000 Hz and the analysis time was 500 msec. Recorded cortical evoked potentials were analyzed and latency (0) and the first positive (P_1–P_3) and negative (N_1–N_3) peaks were measured, as were the peak-to-peak amplitudes (Fig. 1).

Statistics

The statistical significance of changes in SEPs associated with thoracic epidural blockade was evaluated using Student's t-test for unpaired data. Comparison between SEP changes during thoracic and lumbar epidural analgesia (3) were evaluated by Student's t-test for unpaired data. A P value of < 0.05 was considered statistically significant.

Results

Mean spread of analgesia (pin prick) was T-3.5 ± 0.4 to L-2.9 ± 0.4 (mean ± SEM). During thoracic epidural analgesia, a reduction, although statistically not significant ($P > 0.1$), was seen in amplitude of all components of SEP after stimulation at the T-10 and L-1 dermatomes (Table 1). SEP did not disappear in any patient during blockade. The latency of the SEP components remained unchanged after stimulation of both dermatomes (Table 2). The sensory thresholds increased only insignificantly ($P > 0.1$) in both stimulation areas during blockade (Table 1).

Figure 1 shows the mean SEP potentials before and during blockade following stimulation of the T-10 and L-1 dermatomes.

Table 3 shows the changes in SEP after stimulation of the T-10 dermatome during thoracic epidural bupivacaine and lumbar epidural bupivacaine 0.5%, the latter producing analgesia from T-6.8 ± 0.9 to S-5. The results of the lumbar epidural blockade are taken from our previous study (3). We saw no complications or side effects during the study.

Discussion

The results of our study show that SEPs were only slightly affected by thoracic epidural analgesia with 9 ml 0.5% bupivacaine after stimulation of the T-10 and L-1 dermatomes and that SEP did not disappear in any patient during blockade.

In a previous study (3), we showed that lumbar epidural analgesia with about 27 ml 0.5% bupivacaine significantly decreased amplitude and increased latency in most SEP components after stimulation of the L-1 dermatome, with less pronounced SEP blockade at the T-10 dermatome. SEP disappeared in four of eight patients during L-1 stimulation and in two patients during T-10 stimulation (3). Our findings during lumbar epidural bupivacaine administration (3) might be explained by a higher concentration of bupivacaine in the lumbar area compared with the

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Table 1. Effect of Thoracic Epidural Bupivacaine (9 ml, 0.5%) on the Amplitude of the Components of the Early Somatosensory Evoked Cortical Potentials after Stimulation of the L-1 and T-10 Dermatomes, and on the Sensory Threshold

	SEP amplitude (μV)[a]			
	L-1		T-10	
Onset	Before	During	Before	During
P_1	1.6 ± 0.4	1.3 ± 0.5	0.9 ± 0.2	0.8 ± 0.2
N_1	2.2 ± 0.7	2.0 ± 0.6	0.9 ± 0.2	0.9 ± 0.1
P_2	2.2 ± 0.7	1.6 ± 0.5	1.1 ± 0.2	0.8 ± 0.1
N_2	2.6 ± 1.4	2.2 ± 1.1	1.2 ± 0.3	1.1 ± 0.2
P_3	2.5 ± 1.5	2.0 ± 1.0	0.7 ± 0.1	0.6 ± 0.1
N_3	1.7 ± 0.6	1.5 ± 0.6	1.6 ± 0.3	1.2 ± 0.3
Peak to peak	3.6 ± 1.1	3.0 ± 1.0	2.3 ± 0.5	1.9 ± 0.3
Sensory threshold (mA)	2.9 ± 0.4	3.4 ± 0.7	3.7 ± 0.3	4.7 ± 0.6
Stimulation intensity (mA)	11.8 ± 1.8	11.8 ± 1.8	14.9 ± 1.2	14.9 ± 1.2

$P > 0.1$ Before and after injection of bupivacaine.
For explanation of SEP component nomenclature, see Figure 1.
[a]Mean ± SEM.

Table 2. Effect of Thoracic Epidural Bupivacaine (9 ml, 0.5%) on the Latency of Onset and the First Three Positive and Negative Peaks of the Somatosensory Evoked Cortical Potentials

	SEP latency (msec)[a]			
	L-1		T-10	
	Before	During	Before	During
Onset	28 ± 3	27 ± 2	28 ± 3	28 ± 3
P_1	36 ± 4	35 ± 3	36 ± 3	37 ± 4
N_1	47 ± 5	47 ± 3	46 ± 4	47 ± 4
P_2	61 ± 5	61 ± 5	58 ± 5	58 ± 5
N_2	77 ± 3	79 ± 2	74 ± 6	75 ± 6
P_3	95 ± 4	95 ± 2	90 ± 6	90 ± 6
N_3	114 ± 4	112 ± 2	116 ± 8	111 ± 6

$P > 0.1$ before and after injection of bupivacaine at L-1 and T-10 level for all peaks.
For explanation of SEP component nomenclature, see Figure 1.
[a]Mean ± SEM.

thoracic area because of the lumbar placement of the catheter tip. However, in the present study, where the catheter was inserted at the T-10 level, we found only a very minor effect on SEP after T-10 and L-1 stimulation. An explanation for this difference is probably that the amount of bupivacaine injected was too small (9 ml). Nevertheless, a segmental blockade (pin prick) from T-3.5 ± 0.4 to L-2.9 ± 0.4 was obtained in the present study. In our previous study (3), where epidural bupivacaine at L2–3 (26.9 ± 1.5 ml) led to sensory analgesia to T-6.8 ± 0.9, a more effective block of the T-10 dermatome was seen, as evaluated by SEP (Table 3).

To obtain a more sufficient segmental neural blockade, either a larger volume or a higher concentration of thoracic epidural bupivacaine may be necessary.

Table 3. Comparison Between Decrease (Percent) in Amplitude, Increase in Sensory Threshold (Percent) and Increase in Latency (Percent) of SEP Components after Stimulation of the T-10 Dermatome during Lumbar (26.9 ± 1.5 ml) and Thoracic (9 ml) Epidural 0.5% Bupivacaine

	Lumbar	Thoracic	P
Percent increase in SEP latencies (msec)			
Onset	26 ± 12	2 ± 3	$0.1 > P > 0.05$
P_1	26 ± 12	1 ± 3	$0.1 > P > 0.05$
N_1	20 ± 12	2 ± 3	>0.1
P_2	16 ± 13	0 ± 1	>0.1
N_2	18 ± 12	2 ± 1	>0.1
P_3	19 ± 12	0 ± 1	>0.1
N_3	32 ± 13	6 ± 4	$0.1 > P > 0.05$
Percent decrease in SEP amplitudes (μV)			
P_1	38 ± 17	5 ± 14	>0.1
N_1	29 ± 19	−11 ± 25	>0.1
P_2	38 ± 12	15 ± 15	>0.2
N_2	26 ± 19	−1 ± 12	>0.2
P_3	32 ± 27	−10 ± 22	>0.2
N_3	31 ± 23	12 ± 19	>0.5
Peak to peak	51 ± 11	6 ± 3	<0.05
Sensory threshold	55 ± 2	28 ± 4	>0.1

$n = 8$ in both groups (mean ± SEM).
Data from lumbar epidural bupivacaine taken from Lund et al. (3).
For explanation of SEP component nomenclature, see Figure 1.

However, a larger volume of local anesthetic may not be clinically desirable, because unwarranted rostral spread of analgesia impeding respiration and cardiac function may occur. Also, thoracic epidural blockade with a stronger bupivacaine solution (1%) has been evaluated, but is not recommended because of tachy-

phylaxis and urinary retention (4). Incomplete afferent blockade as demonstrated by SEPs in this study during conventional doses of thoracic epidural bupivacaine may explain why the endocrine and metabolic response to upper abdominal surgery may be only partially modified by thoracic epidural analgesia despite clinically acceptable (but not total) pain relief (1,2). In contrast, a pronounced reduction of endocrine and metabolic responses associated with lower abdominal (gynecological) procedures and orthopedic procedures in the lower extremities may be achieved by lumbar epidural bupivacaine (2), which concomitantly leads to a significant inhibition of SEPs to dermatomal electrical stimulation within the area of analgesia (3).

In conclusion, thoracic epidural analgesia with 9 ml 0.5% bupivacaine provides only a limited neural blockade as assessed by early SEPs, despite sufficient blockade as assessed by analgesia to pin prick.

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Epidural Ketamine for Postoperative Pain Relief after Gynecologic Operations:
A Double-Blind Study and Comparison with Epidural Morphine

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KAWANA Y, SATO H, SHIMADA H, FUJITA N, UEDA Y, HAYASHI A, ARAKI Y. Epidural ketamine for postoperative pain relief after gynecologic operations: a double-blind study and comparison with epidural morphine. Anesth Analg 1987;66:735–8.

This double-blind study evaluates whether ketamine given epidurally is effective for postoperative pain relief, and compares the effects of epidural ketamine with those of epidural morphine. Sixty-eight patients undergoing abdominal gynecologic surgery were randomly assigned into six groups (control; ketamine 4, 6, and 8 mg in saline; 6 mg in 10% glucose; morphine 3 mg). All patients were anesthetized with thiopental, nitrous oxide, and enflurane, and drugs were administered epidurally at the end of the operation. The duration of analgesia in the ketamine groups did not differ from that in control patients and the difference in diluent had no observable effects. Significantly, none of the patients in the morphine group needed additional analgesics within 24 hr, whereas 85% in the other five groups did. We conclude that ketamine administered epidurally is inadequate for postoperative pain relief after gynecologic operations.

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—ketamine. ANESTHETICS, INTRAVENOUS—ketamine.

Epidural narcotics are now widely used for postoperative pain relief, but their side effects, especially delayed respiratory depression, are a problem (1,2). Recently Islas et al. reported that 4 mg ketamine administered epidurally was safe and adequate after lower abdominal, perineal, or lower extremity surgical procedures (3). Naguib et al. also reported that 30 mg epidural ketamine was effective for postoperative pain control (4). These studies were not, however, double blinded. We therefore studied in double-blind fashion the usefulness of epidural ketamine for postoperative pain relief after abdominal gynecologic surgery. We also compared epidural ketamine with epidural morphine.

Materials and Methods

Sixty-eight women, ASA physical status I and II, aged 25–65 yr, and undergoing elective abdominal gynecologic surgery were studied. Patients who had disorders of the lumbar spine were excluded. Informed consent was obtained from all the patients, and the study had the approval of the Ethics Committee of the hospital. No patient was receiving narcotics or analgesics at the time of the study.

Thirty–60 min prior to the operation, patients were premedicated with atropine 0.5 mg and hydroxyzine 50 mg given IM. An epidural catheter was inserted at the lumbar epidural space and advanced cephalad a few centimeters. After analgesia produced by a test dose of 2–3 ml 1% mepivacaine confirmed proper location of the catheter, general anesthesia was induced with thiopental and maintained with enflurane and nitrous oxide (50–65%) in oxygen. Neuromuscular blockade was provided with pancuronium. No additional analgesics were used.

Patients were randomly assigned into six groups. Patients in group 1 received only epidural saline 10 ml and served as control. Patients in groups 2–4 received ketamine in saline (total 10 ml) in doses of 4 mg, 6 mg, and 8 mg. Patients in group 5 were given 6 mg ketamine in 10% glucose (total 10 ml) epidurally to determine whether there were differences in ketamine effectiveness when the diluent was changed.

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Table 1. Patient Characteristics and Duration of Anesthesia

Group	Age (yr)	Weight (kg)	Height (cm)	Duration of anesthesia (min)
1 (n = 9)	41.8 ± 8.76	55.4 ± 6.60	158 ± 3.20	164 ± 26.5
2 (n = 12)	38.8 ± 7.86	54.7 ± 6.27	156 ± 4.18	152 ± 30.7
3 (n = 12)	40.7 ± 7.01	54.9 ± 7.69	155 ± 4.78	143 ± 36.5
4 (n = 10)	43.8 ± 7.47	50.6 ± 5.50	154 ± 5.90	152 ± 38.6
5 (n = 8)	41.0 ± 7.71	52.5 ± 6.30	155 ± 3.68	153 ± 36.7
6 (n = 17)	40.5 ± 9.82	52.4 ± 5.90	154 ± 4.31	154 ± 36.7
P	NS	NS	NS	NS

Group 1: saline, 10 ml.
Group 2: ketamine, 4 mg/saline total 10 ml.
Group 3: ketamine, 6 mg/saline total 10 ml.
Group 4: ketamine, 8 mg/saline total 10 ml.
Group 5: ketamine, 6 mg/10% glucose total 10 ml.
Group 6: morphine, 3 mg/saline total 10 ml.
Values are mean ± SD.
NS, not significant.

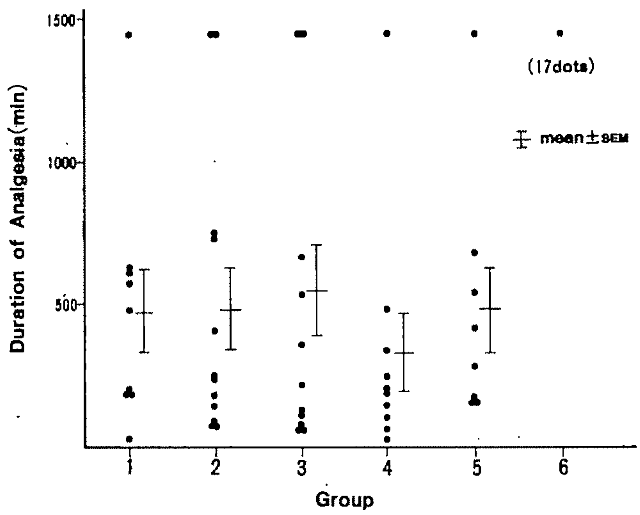

Figure 1. Duration of postoperative analgesia. Group 1, saline 10 ml; group 2, ketamine 4 mg in saline; group 3, ketamine 6 mg in saline; group 4, ketamine 8 mg in saline; group 5, ketamine 6 mg in 10% glucose; group 6, morphine 3 mg in saline.

Patients in group 6 received 3 mg epidural morphine in saline (total 10 ml). The study in groups 1–5 was double-blind. Because of the way in which use of narcotics is regulated, the study in group 6 was not double-blinded, but patients did not know which drugs were being used. When the peritoneum was closed at the end of the operation, enflurane was stopped and the analgesics (or saline) were administered via the epidural catheter.

In the postoperative period, patients were not given special attention as study patients. When the patients asked for analgesics, or if they complained of restricted breathing because of pain, nurses were instructed to administer analgesics (usually pentazocine or buprenorphine) intramuscularly.

Table 2. Side Effects

	K	M	C
Nausea	8/42 (19%)	3/17 (18%)	2/9 (22%)
Nightmares	2/42	0	0
Itching	0	0	0
Headache	0	0	0

Abbreviations: K, ketamine groups (n = 42); M, morphine group (n = 17); C, control (n = 9).

The time between the injection of drugs epidurally and the first dose of analgesics within the first 24 hr was recorded as "duration of postoperative analgesia." If the patient did not need analgesics within that period, the epidural medication was considered to be effective for 24 hr. Side effects such as itching, nausea, headache, and hallucination were evaluated by anesthesiologists upon questioning the patients the next day. The bladder was catheterized in every case, so urinary retention did not occur.

In order to detect the significant differences among groups, Wilcoxon's two-sample rank test and analysis of variance were carried out.

Results

Patient characteristics are summarized in Table 1. There were no statistically significant differences in patient characteristics among groups. Operative procedures included abdominal hysterectomy (43 patients), enucleation of uterine myoma (16 patients), and oophorectomy (nine patients); these were distributed equally among the groups. All incisions were longitudinal lower abdominal incisions. All the patients recovered from the general anesthesia within 40 min of the discontinuation of enflurane.

The duration of postoperative analgesia was not

statistically significantly different between group 1 and groups 2–4 or among the latter three groups. In addition, duration of analgesia did not differ significantly when the diluent was 10% glucose instead of saline (group 5). On the other hand, none of the patients in group 6 needed additional analgesics within the first 24 hr, and the differences between it and the other groups were significant ($P < 0.001$, by Wilcoxon's two-sample rank test) (Fig. 1).

In the ketamine group, eight out of 42 (19%) complained of nausea, whereas three out of 17 (18%) in the morphine group and two out of nine (22%) in the control group did (Table 2). The differences among groups were not significant and could be related to operative procedures or enflurane. Two patients in group 4 complained of nightmares. No patients had itching or headaches and there were no cutaneous allergic responses. Though blood gas tensions were not measured, there were no clinically evident cases of respiratory depression.

Discussion

In 1985 Islas et al. reported that 4 mg ketamine administered epidurally is effective for postoperative pain control (3). Their cases were limited, however, to lower extremity or minor lower abdominal procedures. If epidural ketamine is effective after more major surgery, it would be useful since respiratory depression is unlikely to occur. Naguib et al. used 30 mg ketamine epidurally after cholecystectomy and considered it to be a safe and effective method (4). On the other hand, Ivankovich and McCarthy commented that its usefulness is doubtful after thoracotomy or major surgical procedures (5). Brock-Utne et al. also reported that epidural ketamine, in doses up to 50 mg, did not provide adequate analgesia after surgery, despite their preliminary report on its effectiveness for chronic pain (6–8). The results of the present double-blind study support the latter two opinions.

The mechanism of analgesic action of ketamine is not entirely clear, but its ability to produce lamina-specific suppression of dorsal-horn unit activity has been reported (9). Some investigations suggest that ketamine acts as an opiate agonist (10–12). Though contrary opinions exist (13), if ketamine does act as an opiate agonist at the spinal level in the same way as opioids do, the response will depend upon either absorption from venous plexus, dural permeability, osmolarity, or lipid solubility (2,14,15). Perhaps intrathecal administration, rather than epidural, would provide more effective results (16).

Recently the noradrenergic descending pathway mediated by α-adrenoceptors has been considered to play an important role in morphine-induced analgesia (17–19). Ketamine administered systemically is known to increase the circulating noradrenaline level (20), but little about its effect on noradrenaline content in the brain or spinal cord has been studied. The possibility remains that ketamine has some effect on spinal analgesic systems, as shown by the fact that relatively large doses (50 mg) of ketamine injected intrathecally produced strong surgical analgesia of short duration equally among patients (16). Further fundamental studies on the mechanism of the action of ketamine in spinal analgesic systems are needed.

Studies of postoperative analgesia are very complex, since the "duration of analgesia" is said to depend upon a large number of factors, including nursing staff, differences in wards, and types of operative procedures (21). In the present study, we studied patients from the same hospital and ward with very similar operations and incisions. Even so, there were many variations among patients in groups 1 to 5; yet the results in group 6 were identical. Though group 6 could not be studied in a double-blind manner owing to the way narcotics must be handled, it is apparent that epidural morphine is more potent than epidural ketamine.

In conclusion, this study demonstrates that epidural ketamine is not adequate for postoperative pain relief after gynecologic operations. The effect of epidural ketamine, if any, is too weak and of too short a duration to warrant clinical use. Although there were no adverse effects, we cannot, at this time, recommend epidural ketamine for the relief of postoperative pain after lower abdominal surgery.

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Clinical Pharmacokinetics of Carbonated Local Anesthetics
I: Subclavian Perivascular Brachial Block Model

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SUKHANI R, WINNIE AP. Clinical Pharmacokinetics of carbonated local anesthetics I: subclavian perivascular brachial block model. Anesth Analg 1987;66:739–45.

Fifty healthy adult patients undergoing upper extremity surgery under brachial plexus anesthesia provided by the subclavian perivascular technique were divided into two groups, so that anesthesia provided by 1% lidocaine hydrochloride in one group could be compared with that provided by 1.1% lidocaine carbonate in the other group. Epinephrine, 1:200,000, was added to both solutions just before injection. Carbonated lidocaine reduced the latency of anesthesia by 45% as compared with the hydrochloride salt and produced complete motor block in almost twice as many patients (54 vs 31%). The duration of anesthesia provided by the two agents was virtually identical, as was duration of motor blockade.

Key Words: ANESTHETICS, LOCAL—carbonated, pharmacokinetics. ANESTHETIC TECHNIQUES, REGIONAL—brachial plexus.

It has been nearly 20 yr since Bromage first demonstrated that the use of carbonated solutions of lidocaine in epidural anesthesia, as compared with lidocaine hydrochloride, reduced anesthetic latency by one third and improved the intensity of motor and sensory blockade significantly (1,2). Subsequently, Schulte-Steinberg used carbonated lidocaine for brachial plexus anesthesia and found that it reduced the latency by 72%, as compared with the hydrochloride (3). When Bromage utilized the carbonate for brachial plexus block, he was able to demonstrate only a 42% reduction in latency as compared with the hydrochloride, but he did agree with Schulte-Steinberg that "in practical terms, either figure represents a major saving of time in a busy clinical situation" (4). Both of these studies, however, were carried out comparing carbonated lidocaine, 2.2%, with lidocaine hydrochloride, 2%. Using these concentrations for most techniques of brachial plexus block requires doses of local anesthetic that approach the limits of safety, so the present study was undertaken to compare the relative efficacy of carbonated lidocaine, 1.1%, with lidocaine hydrochloride, 1%. (The seeming discrepancy in the two concentrations is due to the fact that equal volumes of 1% lidocaine hydrochloride and 1.1% lidocaine carbonate are equivalent in terms of lidocaine *base*.) Furthermore, because the mechanism by which carbonated anesthetics increase the speed of onset of anesthesia is poorly understood, the present study also attempts to delineate this mechanism.

Materials and Methods

This prospective, double blind, randomized study was carried out in 50 healthy, consenting, adult patients scheduled to undergo upper extremity surgery under brachial plexus anesthesia. All patients were premedicated with an appropriate dose of morphine given IM to inpatients 30–45 min prior to the anticipated time of the block and IV to outpatients 10–15 min prior to the anticipated time of the block. All patients received a subclavian perivascular brachial plexus block as described elsewhere (5), using a volume of local anesthetic equal in milliliters to half the patient's height in inches, but empirically adding 2–4 ml. Of the 50 patients in the study, 26 received 1% lidocaine hydrochloride and 24 received 1.1% lidocaine carbonate, and in both groups epinephrine 1:200,000 was added to the anesthetic just prior to injection. As soon as the injection of local anesthetic was complete, a stopwatch was started to determine the time of onset and the duration of the resultant sensory and motor blockade.

The onset of sensory blockade was determined by noting the response to pinprick using two endpoints (Table 1). Analgesia was said to exist when the patient

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Table 1. Definition of Modalities

Analgesia	Time of injection to time of loss of pain on pinprick
Anesthesia	Time of injection to time of loss of touch and pressure on pinprick
Paresis	Time of injection to time of onset of motor loss (partial motor block)
Paralysis	Time of injection to time of complete motor loss (complete motor block)
Penetration time	Time of injection to time of proximal paresis
Intraneural diffusion	Time of proximal paresis to time of complete distal sensory block

no longer perceived the pin as sharp, and anesthesia when the patient did not feel the pin at all. Furthermore, the onset of both sensory and motor blockade was determined proximally and distally to allow differentiation of onset in mantle and core fibers. Proximally, the onset of analgesia and anesthesia was determined over the deltoid muscle in the distribution of the axillary nerve and distally in the thumb and little finger in the distribution of the median and ulnar nerves, respectively.

The onset of motor blockade was also determined proximally and distally to allow differentiation of onset in mantle and core fibers. Proximally, the onset of motor blockade, or paresis of the delto-pectoral group of muscles was said to exist when the patient first experienced difficulty in elevating the arm off the table; and the motor block was considered complete, that is, paralysis was said to exist, when the patient could not move the arm at all. Distally, the time to paresis and the time to paralysis were determined in the hand as follows: A pediatric blood pressure cuff placed around the palm of the hand was partially inflated, and the maximal pressure that could be generated by having the patient clench his fist was noted. After the performance of the block, the inability to reach the preblock pressure indicated the onset of motor blockade or paresis, and the inability to move the fingers at all was taken to indicate complete block or paralysis.

Having determined the time required for the onset of analgesia, anesthesia, paresis, and paralysis in the shoulder and hand, the time for penetration (of connective tissue barriers) and the time for intraneural diffusion for the two agents was calculated as follows: From the time of injection to the time of proximal paresis was considered to represent the time for penetration, and the time of proximal paresis to the time of complete distal sensory block was considered to represent the time for intraneural diffusion. Because the axillary and median nerves both contain fibers derived from the superior trunk, and because the superior trunk is the trunk most commonly encountered using the subclavian perivascular technique of brachial plexus block, the calculations for penetration time and intraneural diffusion were made utilizing the data obtained in the distribution of these two nerves (6).

The clinical advantage of any local anesthetic depends, to a large degree, upon the time for the development of full surgical anesthesia. Because anesthesia in the distribution of the inferior trunk will be the slowest to develop with the subclavian perivascular technique of brachial plexus block, the time to onset of analgesia and anesthesia in this distribution was determined as well, because this would represent the time to the onset of surgical anesthesia of the entire extremity.

Finally, the durations of analgesia, anesthesia, paresis, and paralysis were determined at both the proximal and distal levels by noting the time required for each modality to return to normal in both the shoulder and the hand. The results obtained in the two groups were compared and analyzed using a Student's *t*-test and χ^2-analysis. Values were considered significantly different if $P < 0.05$.

Results

The physical characteristics of the patients are represented in Table 2. The time required for the onset of sensory blockade with both agents is presented in Table 3. This is portrayed graphically in Figure 1, which shows that at the level of the shoulder, carbonated lidocaine provides a significantly faster onset of both analgesia and anesthesia than the hydrochloride does. In the hand, in the distribution of the median nerve, the onset of analgesia provided by the two agents is not significantly different, although it is in the ulnar distribution. However, in terms of the onset of anesthesia, the carbonate is significantly faster in the distribution of both nerves.

Table 4 presents the data pertaining to the onset of motor blockade. This is represented graphically in Figure 2, which indicates that there is no significant difference between the two agents with respect to the onset of paresis or paralysis of the shoulder muscle; but in the hand, there is a significant difference between the two agents with respect to the onset of both paresis and the onset of paralysis. The onset of paralysis is significantly faster with the carbonated lidocaine than with the hydrochloride. Furthermore, only 31% of the patients receiving the hydrochloride obtained complete paralysis as compared with 54%

Table 2. Physical Characteristics of the Patients

Drug	Age (yr)	Height (inches)	Weight (km)	Sex (F/M)
Lidocaine-HCl (n = 26)	36.3 ± 13.8	66.9 ± 3.4	68.01 ± 14.3	12/14
Lidocaine-CO_2 (n = 24)	44.7 ± 14.8[a]	67.0 ± 2.6	72.5 ± 14.1	11/13

[a]$P \leq 0.05$.

Table 3. Onset of Sensory Blockade

			Analgesia		Anesthesia	
	Innervation	Site	Lidocaine-HCl (n = 26)	Lidocaine-CO_2 (n = 24)	Lidocaine-HCl (n = 26)	Lidocaine-CO_2 (n = 24)
Proximal distribution	C-5,C-6 (Axillary)	Shoulder	2.69 ± 0.98	1.97 ± 0.63[b]	7.30 ± 3.80	4.27 ± 1.52[c]
Distal distribution	C-6,C-7 (Median)	Hand	3.75 ± 1.50	3.18 ± 1.45	12.42 ± 5.55	8.17 ± 3.84[b]
	C-8,T-1 (Ulnar)	Hand	5.30 ± 3.50	3.28 ± 1.50[a]	18.20 ± 8.11	9.95 ± 3.36[c]

[a]$P \leq 0.05$.
[b]$P \leq 0.01$.
[c]$P \leq 0.001$.

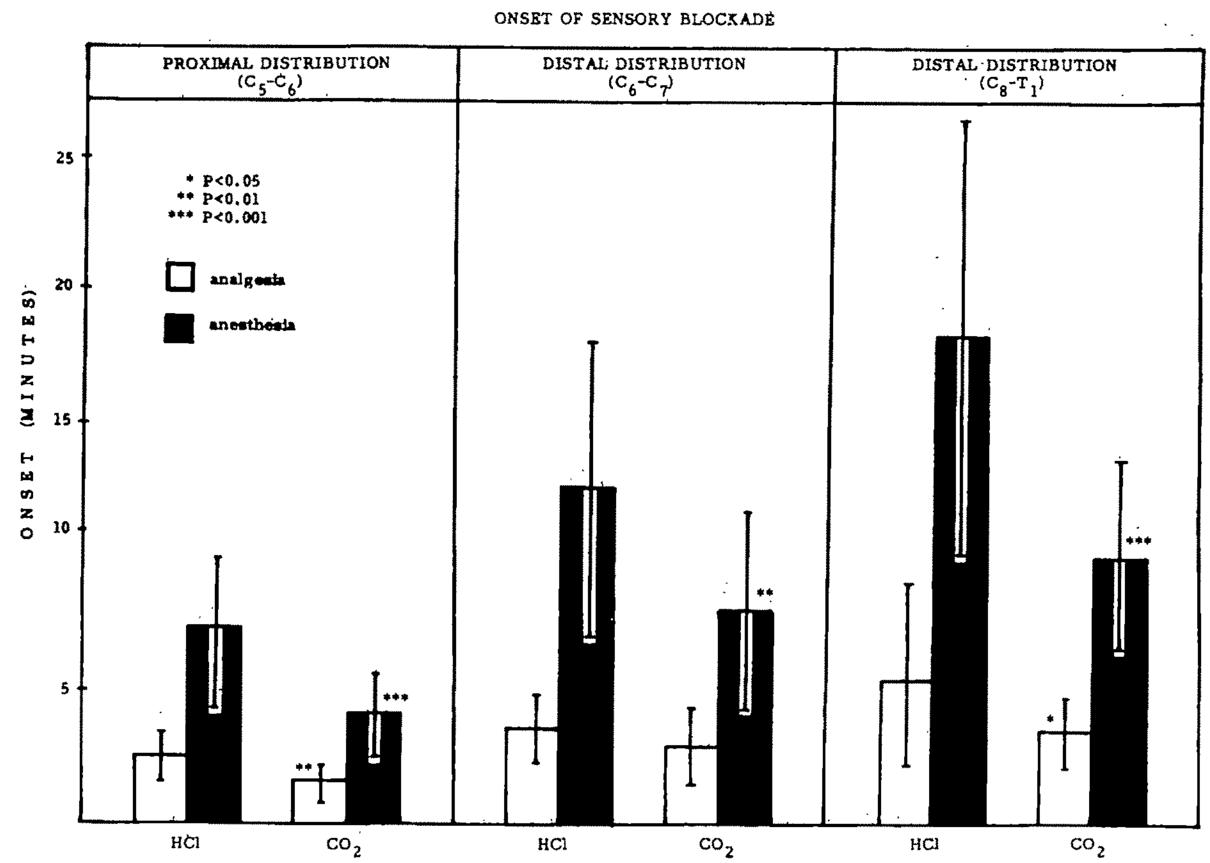

Figure 1. Graphic comparison of the onset of both proximal and distal sensory block. There is statistically significant difference between the two agents with respect to both analgesia and anesthesia, except for the onset of analgesia in C6–C7 distribution.

Table 4. Onset of Motor Blockade

	Site	Paresis: Lidocaine-HCl (n = 26)	Paresis: Lidocaine-CO_2 (n = 24)	Paralysis: Lidocaine-HCl (n = 26)	Paralysis: Lidocaine-CO_2 (n = 24)
Proximal distribution	Shoulder	1.75 ± 0.66	1.39 ± 0.51	4.11 ± 2.91	2.69 ± 2.24
Distal distribution	Hand	3.39 ± 1.58	2.62 ± 1.12[a]	20.75 ± 9.30	10.07 ± 5.21[b]

Only eight patients out of 26 achieved complete distal paralysis in the HCl group.
Only 13 patients out of 24 achieved complete distal paralysis in the CO_2 group.
[a] $P \leq 0.05$.
[b] $P \leq 0.001$.

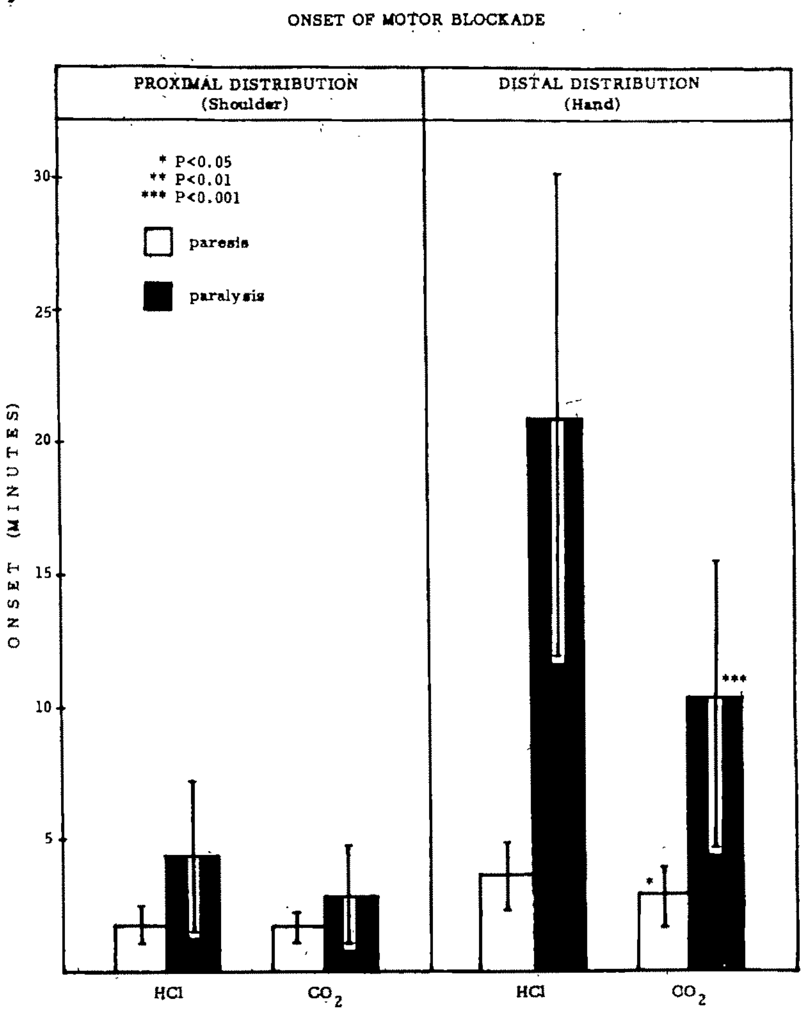

Figure 2. Graphic comparison of the onset of both proximal and distal motor block. There is a statistically significant difference between the two agents with respect to the onset of both paresis and paralysis, but only in the distal musculature.

of the patients receiving the carbonate. This difference however was not statistically significant.

Table 5 presents the calculated rates of penetration and diffusion. This is presented graphically in Figure 3, which indicates that there is a statistical difference between the two agents with respect to both penetration time and intraneural diffusion, with carbonate significantly faster when compared to lidocaine hydrochloride.

Table 5. Rate of Penetration and Diffusion

Drug	Penetration	Intraneural diffusion
Lidocaine-HCl (n = 26)	1.75 ± 0.66	10.67 ± 5.14
Lidocaine-CO_2 (n = 24)	1.39 ± 0.51[a]	6.77 ± 3.56[b]

[a] $P \leq 0.05$
[b] $P \leq 0.01$

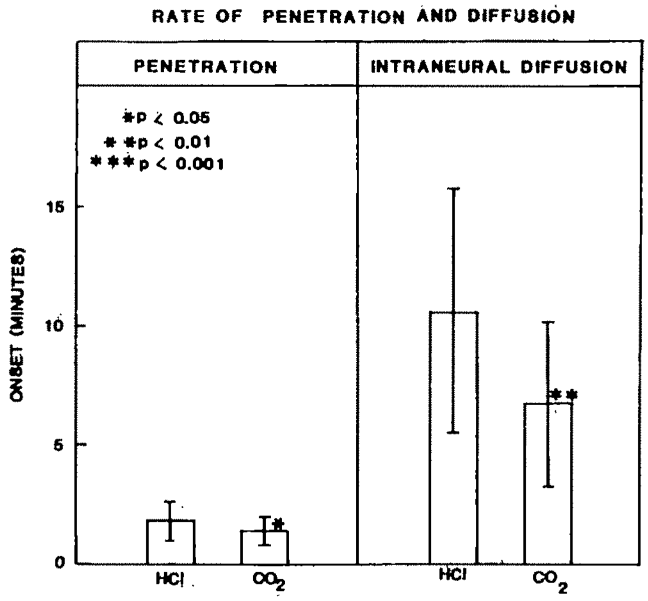

Figure 3. Graphic comparison of the rates of penetration and intraneural diffusion derived from the data obtained in the two groups. Both penetration and intraneural diffusion are faster with the carbonate salt, and the difference is statistically significant.

The pattern of recovery in the present study was identical to that described in previous studies, with distal recovery preceding proximal, and with sensory recovery slightly preceding motor recovery at both levels. As may be seen in Table 6 and Figure 4, the duration of anesthesia provided by the two agents was virtually identical, as was the duration of motor blockade.

Table 6. Duration of Sensory and Motor Blockade

Drug	Duration of sensory blockade (min)	Duration of motor blockade (min)
Lidocaine-HCl	235 ± 15	240 ± 15
Lidocaine-CO_2	230 ± 15	245 ± 20

Discussion

This study corroborates the findings of both Bromage and Schulte-Steinberg that carbonated lidocaine markedly shortens the latency of anesthesia after brachial plexus block for hand surgery. The 45% reduction in latency observed in this study is almost identical to the 42% reduction observed by Bromage. Furthermore, it would appear from the data obtained in the present study that the mechanism by which the onset time is reduced is both more rapid penetration of connective tissue sheaths around the nerve trunk and more rapid intraneural diffusion with the latter having a greater impact than the former. It had been postulated by Schulte-Steinberg that with carbonated lidocaine, the pH is higher than that of the hydrochloride, so little buffering is required, free base is quickly liberated. However, the pH of the lidocaine hydrochloride used in this study was 6.5 and the pH of the carbonate was 6.8, so the difference in pH is not sufficient to explain the more rapid onset. We have used the time from the end of the injection of local anesthetic until the time of the onset of motor blockade in the mantle fibers of the trunks as an index of penetration time because of the fact that the most peripheral nerve fibers at the level of the trunks of the brachial plexus are the motor fibers which are about to leave the trunks to innervate the muscles of the shoulder girdle and upper arm. Conversely, because there are no cutaneous sensory branches that leave the brachial plexus proximal to the distal portion of the cords of the plexus, the sensory fibers lie more centrally at the level of the trunks. Therefore, as a local anesthetic solution penetrates the epineurial barrier, the first fibers encountered are motor, so the blocking process begins in motor fibers before the local anesthetic has even reached any sensory fibers. Similarly, we have used the time from the onset of motor blockade in these peripheral mantle fibers to the time when sensory blockade is complete in the core fibers as an index of intraneural diffusion, because the most central fibers in the core of the nerve trunk are the sensory nerves to the hand (7). Because we wish to look at the diffusion process in a single trunk, the time from the onset of motor blockade in the axillary nerve to the time of complete sensory blockade in the median nerve are utilized to measure intraneural diffusion; these nerves are both derived from fibers in the superior trunk. The additional time required for complete sensory block in the distribution of the ulnar nerve is presumably not due to a slower intraneural diffusion rate within the inferior trunk but due to the fact that the inferior trunk, which contains the fibers that ultimately comprise the ulnar nerve, is at a significantly greater distance from the needle tip than the superior trunk. Thus extraneural diffusion (spread) from needle tip to the inferior trunk must take place before penetration of the connective tissue sheaths can take place and intraneural diffusion can begin. Obviously, this additional time is an important factor clinically, because surgery cannot start until surgical anesthesia of the entire hand is complete. Assuming that intraneural diffusion is approximately the same in the inferior trunk as in the superior trunk, the increased time to complete sensory blockade in the ulnar distribution seen with both agents is most likely a function of the greater distance from the tip of the needle to the inferior trunk.

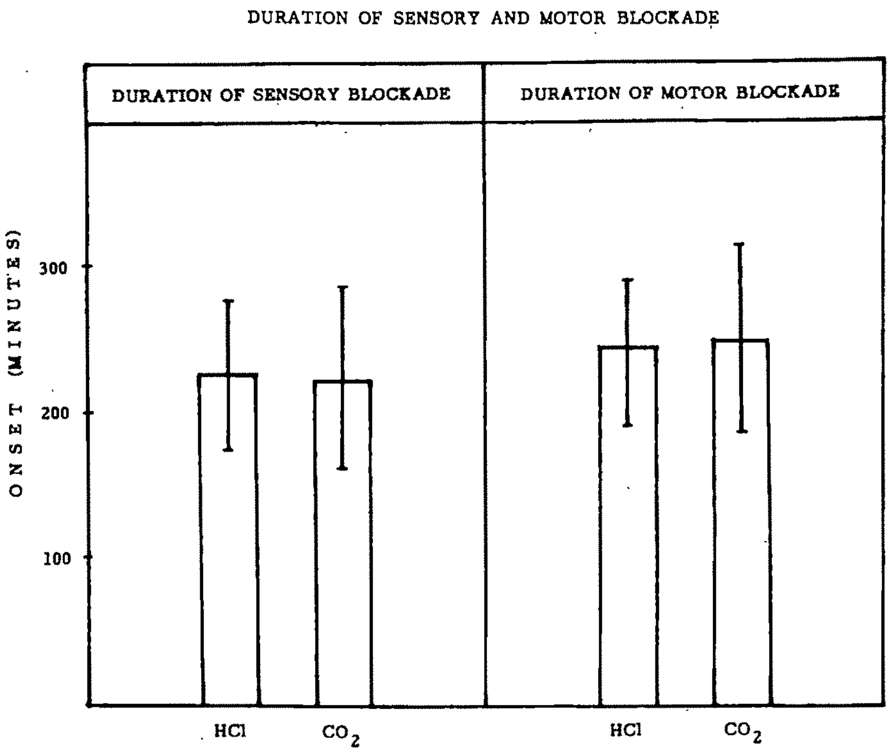

Figure 4. Graphic comparison of the duration of the sensory and motor block provided by the two agents. The differences are not statistically significant.

The high incidence of incomplete distal motor block is for the most part clinically insignificant, for the block was termed incomplete if there was any motion of the fingers whatsoever. Actually, the vast majority of patients in both groups had marked weakness of the hand, i.e., paresis but not paralysis.

Nonetheless, by our criteria there was an increased incidence of complete motor block observed in the group receiving the carbonated lidocaine (54 vs 31% in the hydrochloride group). Whereas Bromage did not compare the intensity of anesthesia in his brachial block studies, he did observe an increased intensity of both motor and sensory block in his epidural studies, an observation recently confirmed by others (8,9). This increased intensity of motor and sensory block provided by the carbonate is attributed to the fact that when the free base of a carbonated solution is liberated, the carbon dioxide produced diffuses very rapidly across a nerve membrane (and, for that matter, across many cell membranes), causing a fall in the intracellular pH and the production of a "cationic trap," which results in a marked increase in the amount of active cation available at the receptor sites on the sodium channels inside the nerve membranes (1). Furthermore, in addition to causing a "cationic trap" carbon dioxide may also have a direct stabilizing effect on the nerve membrane. This stabilizing effect of CO_2 has been demonstrated in animal experiments by Catchlove (10) and Condouris and Shakalis (11).

In our study, the duration of anesthesia was virtually identical with the two agents, which is in agreement with the findings of Schulte-Steinberg, but in disagreement with Bromage's finding that carbonated lidocaine produced a 10% reduction in duration as compared with the hydrochloride. It is important to realize, however, that in the present study, although "complete recovery" required 220–260 min, this does not mean that surgical anesthesia lasted this long. Only analgesia to pinprick persisted for this duration, and indeed, the short duration of surgical anesthesia of the hand is a problem that limits the clinical utility of lidocaine, whether carbonate or hydrochloride, even with epinephrine added.

In short, our present study indicates that when using the subclavian perivascular technique of brachial plexus block for surgery on the hand, carbonated lidocaine provides a significant reduction in the latency of anesthesia as compared with lidocaine hydrochloride, a difference which would appear to be due to a more rapid rate of intraneural diffusion. Furthermore, the carbonated solution produces a greater incidence of complete motor blockade, presumably due to the production of ion trapping and a resultant increase in the amount of active cation available at intraneural receptor sites.

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Changes in Serum Glucose and Serum Growth Hormone Levels during Pituitary Surgery

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MARUYAMA K, MUNEYUKI M, KOJIMA T, HASHIMOTO H, OI Y, OKUDA M, KURIOKA T, FUJITA Y, KONISHI K. Changes in serum glucose and serum growth hormone levels during pituitary surgery. Anesth Analg 1987;66:746–50.

During transsphenoidal surgery, serum growth hormone (GH) and serum glucose levels were measured in five acromegalic patients with diabetes or glucose intolerance, three acromegalic patients without diabetes or glucose intolerance, and six patients with prolactinoma. Preoperative steroid administration produced a significant increase in serum glucose level in acromegalic patients with diabetes or glucose intolerance, whereas in the other two groups no significant change in serum glucose level was found. After surgery started, there was a statistically significant increase in serum glucose level above baseline levels in all three groups. Serum GH levels decreased after commencement of surgery in acromegalic patients, and tumor manipulation did not produce a statistically significant increase in serum GH levels. Simultaneous increases in serum glucose and serum GH levels upon tumor manipulation did not occur in any group. We conclude that preoperative steroid administration in patients with high serum levels of GH in association with diabetes or glucose intolerance increases serum glucose levels, and that, after commencement of surgery, GH has only a minor role in the changes of serum glucose levels.

Key Words: ANESTHESIA—neurosurgery. SURGERY—neurologic. HORMONES—growth.

Endocrine and metabolic responses to surgical procedures result in substrate mobilization. In normal subjects, although serum growth hormone (GH) levels increase during surgery, GH plays only a minor role in the resulting metabolic changes (1). Because in a minority of acromegalic patients diabetes or glucose intolerance may exist preoperatively, GH might affect carbohydrate metabolism during pituitary surgery for acromegaly. The changes in serum GH levels occurring during surgical procedures on GH-secreting tumors and their effects on carbohydrate metabolism in acromegalic patients have not been quantitated. The present study was therefore undertaken to determine serum GH and glucose levels of patients with GH-producing adenoma during transsphenoidal surgery. We also carried out a similar study on patients with prolactinoma.

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Patients and Methods

Fourteen patients undergoing transsphenoidal surgery were studied. Five were acromegalic patients with diabetes or glucose intolerance (group A, three men and two women, aged 51–61 yr, [mean ± SD, 56.6 ± 4.4]), three were acromegalic patients without diabetes or glucose intolerance (group B, two men and one woman, aged 31–49 yr [38.7 ± 9.3]), and six were patients with prolactinoma (group C, one man and five women, aged 28–58 yr [45.2 ± 5.0]). Patients were premedicated with diazepam, 10 mg intramuscularly, and atropine sulfate, 0.5 mg subcutaneously, 1 hr before induction of anesthesia. Infusion of lactated Ringer's solution was started at the same time and hydrocortisone, 300 mg IV, was administered. Anesthesia was induced with 4 mg/kg thiopental, 0.4 mg fentanyl, and 5 mg droperidol, followed by 0.1 mg/kg pancuronium with 50–65% nitrous oxide in oxygen. The trachea was intubated orally and anesthesia then maintained with 50–65% nitrous oxide in oxygen supplemented with enflurane (0.5–1.0%) plus fentanyl, 0.1–0.2 mg IV, every 45–90 minutes after commencement of surgery. The right radial artery was

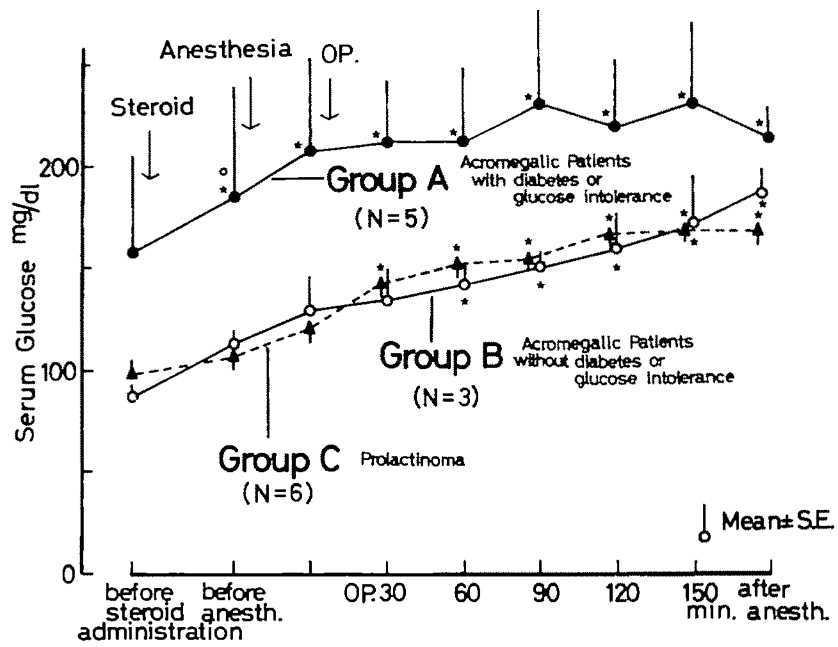

Figure 1. Changes in serum glucose levels. There was no significant difference in baseline levels in the three groups. Steroid administration significantly increased serum glucose level above baseline level in group A. In group B and C, serum glucose level increased significantly after the start of surgery. Throughout the subsequent surgery there was no change in any group and no significant difference among the groups. Abbreviation: OP, start of operation; ★$P < 0.05$ compared to baseline levels; ○$P < 0.05$ compared to immediately preceding level.

cannulated for continuous measurement of arterial blood pressure and for blood sampling. Mechanical ventilation maintained Pa_{O_2} over 100 mm Hg, Pa_{CO_2} at 30–40 mm Hg and pH at 7.30–7.45. Systolic blood pressure was maintained under 140 mm Hg throughout the operation.

Blood sampling for measurement of serum GH was performed: 1) before premedication, 2) immediately before induction of anesthesia, 3) at the beginning of the tumor manipulation, 4) during manipulation of the tumor, 5) after removal of the tumor, and 6) in the postanesthetic period. Sampling for measurement of serum glucose was performed: 1) before premedication and steroid administration, 2) immediately before induction of anesthesia, 3) before commencement of surgery, and 4) every 30 min after the start of surgery.

Arterial blood for measurement of serum glucose levels was centrifuged immediately and serum glucose was measured by the glucose oxidase method within 24 hr. Blood samples for measurement of GH levels were collected in plastic syringes, centrifuged immediately and the serum stored at −20°C until assay. Serum GH was assayed by a double antibody radioimmunoassay. The intraassay coefficient of variation of this method was 4.0%.

Student's *t*-test was used for intragroup changes. The Welch test was used for measurement of the significance of mean differences between groups. $P < 0.05$ was considered to indicate a significant difference.

Results

Serum Glucose

Changes in serum glucose levels are shown in Figure 1. Serum glucose levels before steroid administration were high in three acromegalic patients with diabetes or glucose intolerance; serum glucose levels were within normal limits in the remaining two acromegalic patients with diabetes or glucose intolerance, in all three acromegalic patients without diabetes or glucose intolerance (group B), and in all patients with prolactinoma (group C). There was no significant difference in baseline levels among the three groups, and no significant changes in serum glucose levels were observed in acromegalic patients without diabetes or glucose intolerance (group B) and patients with prolactinoma (group C) given steroid administration and anesthesia before surgery. However, in acromegalic patients with diabetes or glucose intolerance (group A), both steroid administration alone and anesthesia produced significant increases in the serum glucose levels above baseline levels. Surgery was associated with significant increases in mean serum glucose levels above baseline levels in the three groups, but the increases were similar in all three groups. Serum glu-

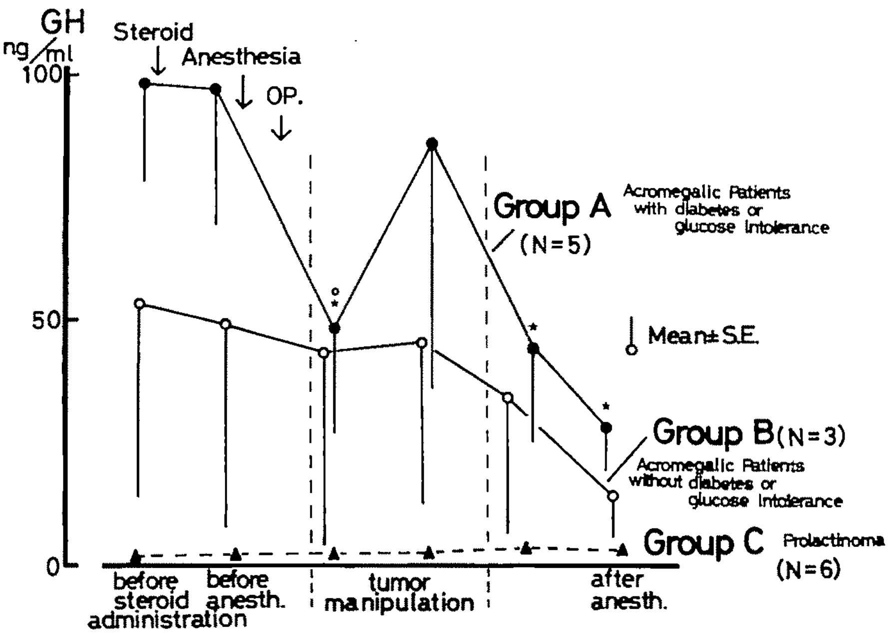

Figure 2. Changes in serum growth hormone (GH) levels. In group A, there were significant decreases in serum GH levels associated with induction of anesthesia as well as after tumor manipulation. An increase in serum GH levels during manipulation of the tumor and a decrease in the levels at the end of manipulation were observed, but these failed to reach statistical significance. ★ $P < 0.05$ compared to baseline levels; ○ $P < 0.05$ compared to immediately preceding level.

cose levels remained elevated but unchanged during surgery in all three groups.

Growth Hormone

The changes in GH levels are shown in Figure 2. Baseline GH levels were within the normal range in patients with prolactinoma and no significant changes occurred with steroid administration, anesthesia, or surgery. In group A acromegalic patients, plasma GH levels were significantly lower at the beginning of tumor manipulation than they were before induction of anesthesia. Increases in serum GH levels during manipulation of the tumor and decreases in the levels at the end of manipulation were observed in patients with acromegaly (groups A and B), but these failed to reach statistical significance.

Discussion

Metabolic responses during anesthesia and surgery are closely related to activation of the hypothalamic–pituitary–adrenal axis. The hypothalamus produces various releasing hormones involved in regulation of sympathetic nervous system activity. In response to surgical stimuli, corticotropin-releasing factor, released from the hypothalamus, causes the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH). ACTH in turn increases the release of cortisol from the adrenal cortex, which increases serum glucose levels. Increased sympathetic nervous system activity also causes the release of catecholamines from the adrenal medulla, in turn further increasing serum glucose levels.

In normal subjects, surgical stimuli are also associated with hypothalamic secretion of GH-releasing hormone that activates the anterior pituitary gland, and an increase in serum GH level (1,2). Although secretion of GH in acromegalic patients is under partial or complete hypothalamic control, despite the presence of high serum growth hormone levels (3,4), changes in serum GH levels during surgical stress in acromegalic patients undergoing surgery in nonhypophyseal areas remain unclear. Furthermore, the changes in serum GH levels occurring during surgical procedures on GH-secreting tumors and their effects on carbohydrate metabolism in acromegalic patients are not known.

Our present results show that, in acromegalic patients with diabetes or glucose intolerance, serum GH levels are significantly lower at the beginning of tumor manipulation than they are before induction of anesthesia. On the other hand, there is no significant change in serum GH levels in patients with prolactinoma. Among the drugs used in this study, administration of steroids and droperidol might have induced this decrease in serum GH levels in acromegalic patients. A variety of drugs can influence the secretion of GH in such patients. Administration of L-dopa, chlorpromazine, haloperidol, dexamethasone, or α-adrenergic blocking agents depresses the secretion of GH in acromegaly (5). Thyrotropin-releasing hormone,

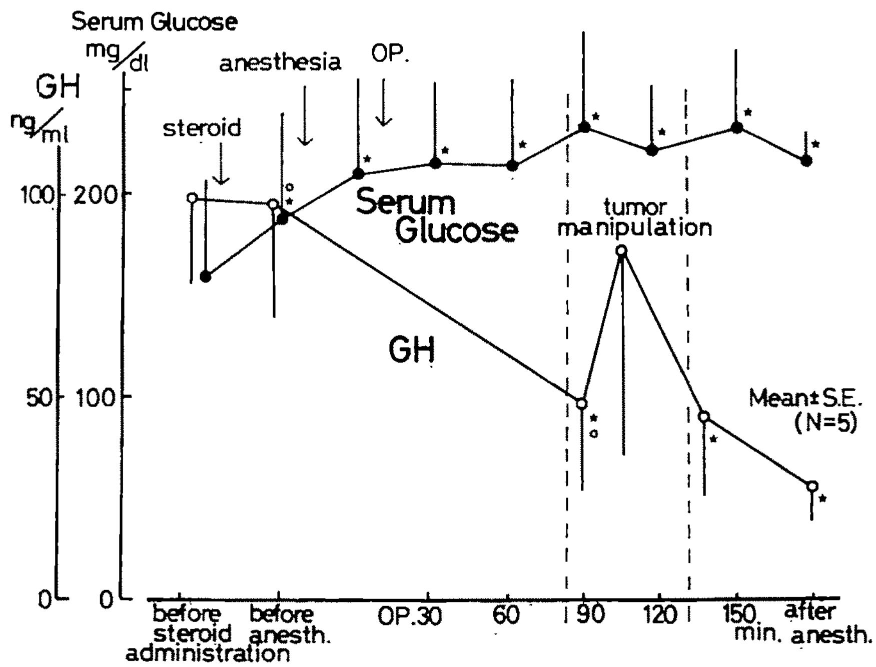

Figure 3. Simultaneous increases in serum glucose and serum GH levels with tumor manipulation did not occur in acromegalic patients with diabetes or glucose intolerance ★ $P < 0.05$ compared to baseline levels; ○ $P < 0.05$ compared to immediately preceding level.

luteinizing hormone-releasing hormone, and *l*-arginine induce secretion of GH in acromegalic patients.

When the anterior pituitary gland is partially or completely destroyed or excised in a surgical procedure, the serum levels of GH in individual patients may be elevated or depressed by surgical manipulation of the tumor. Our data show nonsignificant increases in serum GH levels during manipulation of the tumor and insignificant decreases at the end of manipulation.

In normal subjects, GH is said to play a minor role in the metabolic changes that occur during surgery (1). However, human GH causes deterioration of diabetes mellitus when given to diabetic patients (5,6). In hypophysectomized juvenile diabetics, administration of a very small amount of GH causes hyperglycemia, glucosuria, and metabolic acidosis (6). Thus, in at least one disease, GH may play a significant role in carbohydrate metabolism. It is therefore important to study the changes in serum glucose levels occurring during surgery on the pituitary gland producing GH in acromegalic patients. Moreover, the patients undergoing pituitary surgery are given steroids (7). Our results show that steroids alone significantly increased serum glucose levels above baseline level in acromegalic patients with diabetes or glucose intolerance (group A). However, in acromegalic patients without diabetes or glucose intolerance (group B) and in patients with prolactinoma (group C), serum glucose levels increased significantly above baseline levels only after commencement of surgery. The combination of high serum GH level and steroid administration may affect carbohydrate metabolism in acromegalic patients with diabetes or glucose intolerance. But the degree of the increase in serum glucose levels in such patients is not as important clinically because there was no significant difference in serum glucose level among the present three groups throughout the subsequent surgery. Simultaneous hyperglycemia and elevation of serum GH did not occur with tumor manipulation in any of the three groups (Fig. 3). These data suggest that surgical stimuli produce a similar degree of effect on carbohydrate metabolism in both acromegalic and prolactinoma patients.

We conclude that the increase in serum glucose level evoked by steroid administration in acromegalic patients with diabetes or glucose intolerance is related to persistent high blood levels of GH. However, after the start of surgery GH plays as minor a role in the metabolic changes in acromegalic patients as it does in normal subjects.

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Effect of Meperidine on Oxygen Consumption, Carbon Dioxide Production, and Respiratory Gas Exchange in Postanesthesia Shivering

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MACINTYRE PE, PAVLIN EG, DWERSTEG JF. Effect of meperidine on oxygen consumption, carbon dioxide production, and respiratory gas exchange in postanesthesia shivering. Anesth Analg 1987;66:751–5.

Meperidine has been used to suppress postanesthesia shivering. However, its efficacy to date has only been assessed by observation of visible shivering. We measured the effect of meperidine on oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$) and pulmonary gas exchange in 14 otherwise healthy patients shivering after general anesthesia. Meperidine successfully suppressed visible shivering in all patients and was associated with significant decreases in $\dot{V}O_2$, and $\dot{V}CO_2$ and minute ventilation ($\dot{V}_E$) but not with return to basal levels. Arterial P_{CO_2} levels remained unchanged at normal, whereas significant improvements occurred in pH and bicarbonate levels. Meperidine is an effective method of reducing the elevated metabolic demand of shivering.

Key Words: COMPLICATIONS—shivering. ANALGESICS—meperidine.

Shivering after general anesthesia increases oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) by up to 500% above basal levels (1–4). Cardiac output ($\dot{Q}_t$) may not increase in proportion to the elevated metabolic demand (1,2). Whereas in otherwise healthy patients minute ventilation ($\dot{V}_E$) increases in accordance with metabolic requirements during shivering (1), patients with diminished cardiopulmonary reserves may not be able to compensate as effectively. Thus, avoidance of postoperative shivering is desirable.

A variety of drugs has been used to control postanesthesia shivering, including methylphenidate (5,6), orphenadrine (7), magnesium sulphate (6), pancuronium (2), metocurine (3), and the opiates, fentanyl, morphine, and meperidine (2,4,8,9). Meperidine appears to be the most effective in spontaneously breathing patients (2,8,9). Claybon et al. (8) report that 25 mg of meperidine arrested shivering within 5 min in 73% of patients and 50 mg of meperidine was successful in 89% of patients. Of the patients that receive saline as a control, 8% stopped shivering within 5 min. The difference was highly significant ($P < 0.001$). To date, however, its efficacy has only been assessed by the observation of visible shivering, not by quantifying changes in $\dot{V}O_2$. Also of concern is that suppression of shivering by a narcotic may cause ventilatory depression and elevation in arterial P_{CO_2} levels.

The purpose of the study was to measure the efficacy of meperidine in reducing the metabolic responses to postanesthesia shivering and to compare pulmonary gas exchange during shivering and after visible shivering had been suppressed by treatment with meperidine.

Methods

Approval for the study was given by the University of Washington Human Subjects Review Committee. Fourteen ASA physical status I patients who had undergone elective, nonthoracic, nonabdominal surgery and who entered the recovery room shivering were studied. No attempt had been made to standardize preoperative medication or anesthetic technique. All endotracheal tubes had been removed.

The patients breathed air through a conventional disposable anesthetic face mask that was adjusted to ensure an airtight fit as attested to by the fact that no nitrogen was detected by mass spectrometry with in-

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Table 1. Summary of Results

	Shivering	After meperidine	P
Oxygen consumption ($L \cdot min^{-1} \cdot 70\ kg^{-1}$ STPD)	0.93 ± 0.36	0.38 ± 0.16	<0.00001
CO_2 production ($L \cdot min^{-1} \cdot 70\ kg^{-1}$ STPD)	0.81 ± 0.34	0.34 ± 0.15	<0.00001
Respiratory quotient	0.86 ± 0.09	0.90 ± 0.08	NS
Minute volume ($L \cdot min^{-1} \cdot 70\ kg^{-1}$ BTPS)	25.50 ± 9.27	12.06 ± 5.02	<0.00001
Tidal volume (L/70 kg BTPS)	1.11 ± 0.39	0.64 ± 0.21	<0.0002
Respiratory frequency (breaths/min)	24.71 ± 7.86	19.14 ± 5.82	<0.0001
Dead space, physiologic	0.32 ± 0.12	0.37 ± 0.09	<0.02
pH	7.324 ± 0.044	7.371 ± 0.048	<0.001
HCO_3 (mmol/L)	21.5 ± 2.04	22.7 ± 2.49	<0.005
Pa_{CO_2}, room air (mm Hg)	41.19 ± 4.11	40.06 ± 4.25	NS
Pa_{O_2}, room air (mm Hg)	77.18 ± 17.75	82.17 ± 17.95	NS
Pa_{O_2}, 100% O_2 (mm Hg)	384.1 ± 120.8	411.7 ± 108.0	NS
$A\text{-}aD_{O_2}$, room air (mm Hg)	23.13 ± 18.73	25.15 ± 18.47	NS
$A\text{-}aD_{O_2}$, 100% O_2 (mm Hg)	285.0 ± 120.5	259.0 ± 109.4	NS

Abbreviations: STPD, standard temperature and pressure dry; BTPS, body temperature pressure saturated.
All data presented as mean ± SD.

spiration of 100% oxygen. A Ruben nonrebreathing valve channeled exhaled gases through a mixing chamber designed to permit continuous mixed expired gas tension measurements. Expired minute volume ($\dot{V}_E$) and respiratory rate (f) were displayed on a Bourne spirometer. A multichannel mass spectrometer (Perkin-Elmer 1100) enabled continuous measurement of inspired and mixed expired oxygen, mixed expired carbon dioxide, and end-tidal carbon dioxide concentrations. Rectal temperature during and after shivering, ambient temperature and barometric pressure, and the temperature of the expired gases were recorded. A sample of arterial blood was taken with the patient breathing room air and again with the patient breathing 100% oxygen after the end-tidal nitrogen concentration had fallen to zero. Arterial gas analysis was performed using the Corning 170 blood gas analyzer. Data were accepted only if the respiratory exchange ratio (RQ) fell between 0.7 and 1.0, both during and after shivering, which we have taken to indicate a steady state—the normal range being 0.7–1.0 (10).

After data had been collected during shivering, an intravenous bolus of meperidine, 25 mg, was administered. If shivering persisted after 5 min, a second dose was administered. All of the above measurements were repeated 5–10 min after cessation of visible shivering.

Oxygen consumption, $\dot{V}CO_2$, alveolar P_{O_2} and dead space (V_D/V_T) were calculated from standard formulas (10). Oxygen consumption and $\dot{V}CO_2$ were corrected to $ml \cdot min^{-1} \cdot 70\ kg^{-1}$ STPD. Basal levels of $\dot{V}O_2$ and $\dot{V}CO_2$ were calculated from the data of Nunn (10) and normalized to 70 kg. Minute ventilation was converted to $ml \cdot min^{-1} \cdot 70\ kg^{-1}$ BTPS and tidal volume (V_T) converted to ml/70 kg BTPS. The effect of meperidine on all measurements was analyzed using the paired Student's *t*-test.

Results

Fourteen patients (12 men and two women) were studied. All patients had received a volatile anesthetic agent (eight isoflurane, four enflurane, two halothane) and nine were given narcotic (eight fentanyl, one morphine) during their anesthesia.

Meperidine, 25 mg IV, successfully suppressed visible shivering within 5 min of injection in 11 of the patients. The remaining three stopped shivering after the administration of an additional 25 mg IV. No patient suffered any side effects from meperidine; in particular, there was no respiratory depression or nausea and vomiting. The results are summarized in Table 1 and Figure 1.

In shivering patients, $\dot{V}O_2$ (0.93 ± 0.36 $L \cdot min^{-1} \cdot 70\ kg^{-1}$) and $\dot{V}CO_2$ (0.81 ± 0.34 $L \cdot min^{-1} \cdot 70\ kg^{-1}$) were 380% above the calculated basal value (Fig. 1). Basal values were determined from the data of Nunn for sedated patients of average build and 20–40 yr of age (10). The patient with the highest metabolic requirement during shivering had $\dot{V}O_2$ and $\dot{V}CO_2$ values of 1.79 and 1.68 $L \cdot min^{-1} \cdot 70\ kg^{-1}$, respectively—more than 730% above basal levels.

The injection of meperidine was followed by significant ($P < 0.00001$) reductions in both $\dot{V}O_2$ (0.38 ± 0.16 $L \cdot min^{-1} \cdot 70\ kg^{-1}$) and $\dot{V}CO_2$ (0.34 ± 0.15 $L \cdot min^{-1} \cdot 70\ kg^{-1}$). Although visible shivering was observed to have ceased, these figures are still greater than 150% of expected basal levels (Fig. 1).

Minute ventilation increased markedly during shivering (25.20 ± 9.27 $L \cdot min^{-1} \cdot 70\ kg^{-1}$), the mean being more than 400% above basal values. Normal

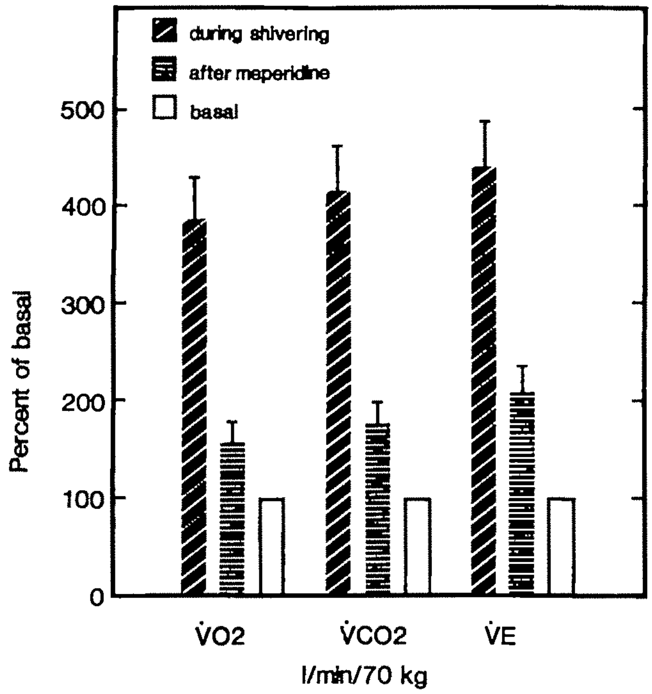

Figure 1. $\dot{V}O_2$ (STPD), $\dot{V}O_2$ (STPD), and $\dot{V}$E (BTPS) expressed as a percentage of expected basal values during shivering and after suppression of shivering by meperidine. Data presented as mean ± SEM.

arterial P_{CO_2} (Pa_{CO_2}) values indicated that alveolar ventilation was adequate in all cases for the increase in metabolic demand. The highest $\dot{V}$E recorded during shivering was 44.6 L·min^{-1}·70 kg^{-1} in the patient with the highest $\dot{V}O_2$ and $\dot{V}CO_2$. The highest $\dot{V}$T measured during shivering was 1.71 l/70 kg and the highest respiratory rate (*f*) was 43 breaths/min.

The administration of meperidine was followed by a significant ($P < 0.00001$) decrease in $\dot{V}$E effected by reductions in both VT and *f*. The Pa_{CO_2} levels remained unchanged and normal, indicating that although meperidine significantly reduced the metabolic requirements of shivering, it did not result in respiratory depression.

A metabolic acidosis seen in all patients improved after visible shivering had been attenuated by meperidine as indicated by significant increases in pH ($P < 0.001$) and serum bicarbonate (HCO_3^-) ($P < 0.005$).

The ratio between dead space (including apparatus dead space) and tidal volume increased significantly after shivering had ceased ($P < 0.02$).

The arterial P_{O_2} levels in shivering patients breathing room air were below normal (77.18 ± 17.75 mm Hg) and decreased to 44.6 mm Hg in one patient. These values did not improve significantly after cessation of shivering, but in the five shivering patients who had Pa_{O_2} levels less than 75 mm Hg, Pa_{O_2} increased in three after administration of meperidine. Similarly, when the $F_{I_{O_2}}$ was 1.0 no improvement in mean Pa_{O_2} was seen after visible shivering had ceased. The alveolar–arterial oxygen differences (A-aD_{O_2}) showed no change after the administration of meperidine whether the patient was breathing room air or 100% O_2.

Discussion

The incidence of postanesthesia shivering varies from 0 to 50% (11–15). Opinions vary as to whether shivering represents a response to lowered body temperature (11,12) or recovery of spinal activity before the upper motor neurons have recovered from the inhibition produced by general anesthesia (5,11,14). Shivering is not the same as muscle spasticity, which may occur in a large number of patients (up to 90%) and seems to be part of the normal pattern of recovery from a general anesthetic (11,14). Shivering has been defined as a rhythmic contraction of muscle groups with irregular intermittent periods of relaxation (14). Although shivering is usually described as a visible phenomenon, Pflug et al. (13) detected subclinical shivering in some of their patients by means of a mercury strain gauge and electronic recorder.

Our study supports previous findings that shivering leads to a marked rise in $\dot{V}O_2$ and $\dot{V}CO_2$ (1–4) and that this is accompanied by an increase in $\dot{V}$E sufficient to meet the elevated metabolic demand (1). Our study also confirms that meperidine is successful in suppressing visible postanesthesia shivering.

Administration of meperidine significantly reduced the $\dot{V}O_2$ and $\dot{V}CO_2$ and effectively reduced the metabolic cost of shivering. That reductions were not to expected basal levels may mean ongoing nonvisible shivering or muscle spasticity despite cessation of visible shivering. In the study by Bay et al. (1) patients did not serve as their own control and the comparison of metabolic demand in shivering and nonshivering patients was made in two separate groups of patients. The $\dot{V}O_2$ and $\dot{V}CO_2$ values for the group who did not shiver were near basal levels. Values for the expiratory exchange ratio in their study that decreased to levels as low as 0.530 may indicate a lack of steady state while measurements were being made. Kaplan and Guffin (2) studied a group of patients shivering after elective coronary artery bypass surgery. The mean $\dot{V}O_2$ during shivering was only 0.298 L/min and it decreased to 0.195 L/min after treatment with meperidine or pancuronium. The highest $\dot{V}O_2$ we recorded during shivering was more than 730% above

expected basal values and was higher than the previously recorded maximum of nearly 500% of basal values (1–4).

The significant decrease in $\dot{V}_E$ after meperidine accorded with the decrease in oxygen demand, but the dose of meperidine used and the decrease in $\dot{V}_E$ did not cause respiratory depression, as evidenced by normal, unchanged arterial P_{CO_2} levels.

Data by Kaplan and Guffin (2) suggest that in some patients cardiac output ($\dot{Q}_t$) may not increase when $\dot{V}_{O_2}$ is increased by shivering and consequently mixed venous oxygen saturation ($S\bar{v}_{O_2}$) is reduced. In their study, changes in $S\bar{v}_{O_2}$ correlated with changes in $\dot{V}_{O_2}$ but not with $\dot{Q}_t$. In our study, a metabolic acidosis seen in the shivering patient improved significantly and rapidly after meperidine, suggesting an improvement in the oxygen supply/demand ratio. Two patients with an arterial pH of less than 7.30 while shivering (7.230 and 7.264), levels that may cause clinical concern, improved to 7.320 and 7.304, respectively, within minutes of meperidine administration.

The V_D/V_T increased after cessation of shivering, a finding not consistent with that of Bay et al. (1). Our findings may be expected if the anatomic and apparatus dead spaces remained relatively constant while the alveolar portion of the tidal volume decreased. Unlike Bay et al., we compared changes in V_D/V_T in the same patient during and after shivering.

When breathing room air, the Pa_{O_2} values in the shivering patient were low. A decrease in Pa_{O_2} (and an increase in $A\text{-}aD_{O_2}$) may result from ventilation–perfusion mismatch or from shunting; however, our patients did not have clinical evidence of lung disease and the nature of their surgery is not likely to produce marked changes of this nature. Kaplan and Guffin (2) noted that the $S\bar{v}_{O_2}$ can decrease in the shivering patient, which would lead to a decrease in Pa_{O_2}. Nitrous oxide was not detected by the mass spectrometer in our study and was not a cause of the hypoxia. There was no statistically significant improvement in Pa_{O_2} after the administration of meperidine. However, of the five shivering patients who had Pa_{O_2} levels less than 75 mm Hg when breathing room air, three had clinically important increases in Pa_{O_2} after the administration of meperidine. When the $F_{I_{O_2}}$ was 1.0, there was again no significant improvement in Pa_{O_2} after the injection of meperidine. Bay et al. (1) also recorded no difference in Pa_{O_2} between shivering and nonshivering patients. They did, however, note a significantly smaller $A\text{-}aD_{O_2}$ in the nonshivering patient and we did not. There was no difference in arterial P_{O_2} and P_{CO_2} levels between their two groups and in some patients a low respiratory exchange ratio may have indicated a lack of steady state, therefore calculation of the $A\text{-}aD_{O_2}$ may not be accurate.

Our patients were all ASA 1 and were able to compensate for the increase in metabolic rate associated with shivering. Kaplan and Guffin (2) have already demonstrated that certain patients who shiver are unable to increase their cardiac output sufficiently to meet the elevation in metabolic demand. There are other patients in whom attempts at compensation may be inadequate. This group may include patients with severe chronic obstructive pulmonary disease (COPD) and patients who already have greatly elevated basal metabolic rates, such as those with large burns. In the latter, both minute ventilation and cardiac output will already be markedly elevated and it may not be possible to meet further demands on the cardiopulmonary reserves.

In patients with severe COPD, ventilatory requirements are already increased by a high physiologic dead space and an increase in the alveolar–arterial oxygen difference. An increase in oxygen consumption due to shivering may precipitate ventilatory failure.

In summary, meperidine effectively reduces increased $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ demands associated with shivering although the reductions are not to basal levels. Metabolic acidosis seen while shivering is also significantly and rapidly improved. The dose of meperidine producing these results does not cause respiratory depression.

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A Comparison of *d*-Tubocurarine Pretreatment and No Pretreatment in Obstetric Patients

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COOK WP, SCHULTETUS RR, CATON D. A comparison of *d*-tubocurarine pretreatment and no pretreatment in obstetric patients. Anesth Analg 1987;66:756–60.

The effect of pretreatment with d-tubocurarine on the incidences of succinylcholine-induced fasciculations and postoperative muscle pain, and the time to onset of and 50% recovery from neuromuscular blockade were studied in 75 obstetric patients. Thirty women with term pregnancies undergoing general anesthesia for elective cesarean section or cesarean section indicated by cephalopelvic disproportion were randomly assigned to two groups. Group C-1 patients received 0.05 mg/kg of d-tubocurarine followed by 1.5 mg/kg of succinylcholine, and group C-2 patients received 1 ml of normal saline followed by 1 mg/kg of succinylcholine. An investigator, unaware of the relaxant regimen used, judged severity of fasciculations and postoperative muscle pain and measured times to onset of and 50% recovery from neuromuscular blockade. This same study design was followed in a group of 30 women undergoing tubal ligation 1 day after vaginal delivery (groups T-1 and T-2). The incidence of both fasciculations and postoperative muscle pain was low and was not significantly different between pretreated and nonpretreated groups. Time to 100% twitch depression was also not significantly different between pretreated and nonpretreated groups. Time to 50% recovery from neuromuscular blockade was significantly longer in both nonpretreated groups (C-2 and T-2). An additional group of 15 patients undergoing general anesthesia for cesarean section using 0.7 mg/kg of succinylcholine without d-tubocurarine pretreatment was studied (group C-3). This smaller dose of succinylcholine produced onset and 50% recovery times similar to the group pretreated with d-tubocurarine (group C-1). We conclude that if doses of succinylcholine are selected properly, there is no difference in the incidence of fasciculations or postoperative muscle pain, nor in the times to onset of or 50% recovery from succinylcholine-induced neuromuscular blockade in obstetric patients either pretreated or not pretreated with 0.05 mg/kg of d-tubocurarine.

Key Words: ANESTHESIA—obstetric. NEUROMUSCULAR RELAXANTS—*d*-tubocurarine, succinylcholine.

In obstetric anesthesia, *d*-tubocurarine is often used for pretreatment before succinylcholine administration (1). Those who use *d*-tubocurarine for pretreatment cite as desirable characteristics the elimination of postoperative muscle pain, fasciculations, and increased intragastric pressure caused by fasciculations. Those who do not use *d*-tubocurarine pretreatment claim that postoperative muscle pain is rare and fasciculations from succinylcholine are minimal in obstetric patients (2,3). In addition, some patients may be sensitive to small doses of *d*-tubocurarine and may experience double vision, inability to swallow, and a feeling of being unable to breathe. Pretreatment with *d*-tubocurarine antagonizes the action of succinylcholine (4) and leads to poor relaxation and difficult intubating conditions. To overcome the interference with paralysis caused by *d*-tubocurarine, succinylcholine dosage is increased (5,6). Also, pretreatment may delay onset of succinylcholine-induced neuromuscular blockade (7).

Some studies (8–10) suggest that the incidences of fasciculations and postoperative muscle pain from succinylcholine are reduced in pregnancy and therefore, pretreatment should not be needed. However, these studies were performed with dosage regimens that are not used in clinical practice (e.g., all patients received a fixed dose of succinylcholine regardless of body size) and some patients were only in the first trimester of pregnancy.

Bryson and Ormston (11) found that pretreatment with gallamine did not reduce the incidence of postoperative muscle pain in patients undergoing cesarean section. Whether *d*-tubocurarine pretreatment would reduce the incidence of postoperative muscle pain or fasciculations in parturients has not been studied.

This study was undertaken to determine the effects

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Table 1. Comparison of Demographic Data of Patients Undergoing Either Cesarean Section or Tubal Ligation

	d-Tubocurarine pretreatment (0.05 mg/kg)	Succinylcholine (mg/kg)	Age (yr)	Weight (kg)	Time since delivery (hr)
Cesarean section					
C-1	Yes	1.5	25.3 ± 6.7	79.1 ± 20.9	—
C-2	No	1.0	24.2 ± 3.5	82.2 ± 20.0	—
C-3	No	0.7	24.2 ± 3.0	83.6 ± 18.8	—
Tubal ligation					
T-1	Yes	1.5	26.2 ± 4.8	75.3 ± 16.4	16.8 ± 7.1
T-2	No	1.0	29.3 ± 5.1[a]	75.4 ± 13.3	15.0 ± 8.6

Values are means ± SD; n = 15 for all groups.
[a]Varies significantly ($P < 0.05$) from groups C-2 and C-3.

of pretreatment with *d*-tubocurarine on the times to onset of and recovery from succinylcholine-induced neuromuscular blockade and on the incidences of fasciculations and postoperative muscle pain using clinically relevant doses in term obstetric patients.

Materials and Methods

An institutional review board approved the experimental design and informed consent was obtained from all patients. Women who had recently received drugs known to alter neuromuscular blockade (e.g., local anesthetics, antibiotics, $MgSO_4$, etc.) were excluded from the study. Thirty women, ASA physical status 1 or 2, with term pregnancies and undergoing general anesthesia for repeat cesarean section or cesarean section indicated by cephalopelvic disproportion were randomly assigned to one of two groups, C-1 or C-2. All patients were orally premedicated with 30 ml of 0.3 M sodium citrate. Prior to induction, an arm of each patient was secured to a board and an FT03 force displacement transducer was positioned to measure adductor pollicis muscle twitch strength (12). With the hand relaxed, thumb adduction tension was adjusted to 50–150 g. Patients in group C-1 received 0.05 mg/kg of *d*-tubocurarine 3 min prior to 5 mg/kg of thiopental and 1.5 mg/kg of succinylcholine. Patients in group C-2 received approximately 1 ml of normal saline 3 min prior to 5 mg/kg of thiopental and 1 mg/kg of succinylcholine. All drugs were rapidly injected into the distal port of a rapidly infusing IV. Cricoid pressure was maintained from time of loss of consciousness until tracheal intubation was confirmed.

After induction, supramaximal square-wave ulnar nerve stimulation at 0.2 Hz (duration of 0.25 msec) was delivered by a Professional Instruments NS-2C nerve stimulator (output verified by an oscilloscope) via surface electrodes placed 6 cm apart at the wrist, with the negative lead placed distally (13). In order to allow sufficient time to demonstrate supramaximal nerve stimulation (no further increase in twitch height with increasing voltage), succinylcholine was administered 20 sec after thiopental. The times from succinylcholine administration to 100% twitch depression and from 100% twitch depression to 50% recovery of control twitch height were recorded. Fasciculations were judged as grade 1 if they were absent or involved minimal periorbital, perioral, or finger-tip movements, and as grade 2 if any extremity or truncal movement was detected.

After intubation, anesthesia was maintained with 0.5% isoflurane and 50% N_2O in O_2 until delivery, whereupon isoflurane was discontinued, N_2O concentration was increased to 60%, and fentanyl citrate, 2–3 μg/kg IV, was given. Ventilation was adjusted so that end-tidal CO_2 was maintained at 30 ± 3 mm Hg, as measured by mass spectroscopy.

All patients were visited 1 day after surgery and allowed to volunteer information about muscle pain. References to incisional, abdominal, or low back pain were ignored. If the patient did not spontaneously mention muscle pain, she was asked specifically if any muscle pain was present, and if so, its location. The classification of fasciculations, presence or absence of postoperative muscle pain, and measurement of twitch height depression and recovery were performed by a single investigator (WPC) who was unaware of the muscle relaxant regimen given patients.

This same study design was then repeated with two groups of 15 patients (groups T-1 and T-2) undergoing tubal ligation the day after uncomplicated vaginal delivery. Analyses of the results from groups C-1, C-2, T-1, and T-2 demonstrated that the administration of 1 mg/kg of succinylcholine without *d*-tubocurarine pretreatment resulted in a longer recovery time. Because a reduction in the dose of succinylcho-

Table 2. Incidences of Grade 2 Fasciculations and Postoperative Muscle Pain

	d-Tubocurarine pretreatment (0.05 mg/kg)	Succinylcholine (mg/kg)	Grade 2 fasciculations		Postoperative muscle pain	
			Percent	n	Percent	n
Cesarean section						
C-1	Yes	1.5	6.7	1	13	2
C-2	No	1.0	13.3	2	13	2
C-3	No	0.7	6.7	1	13	2
Tubal ligation						
T-1	Yes	1.5	6.7	1	13	2
T-2	No	1.0	6.7	1	13	2

n = 15 for all groups.

line given without pretreatment might result in a recovery period similar to that obtained with pretreatment, an additional group of 15 patients undergoing general anesthesia for elective cesarean section and receiving 0.7 mg/kg of succinylcholine without *d*-tubocurarine pretreatment was studied (group C-3).

Age and weight were compared among all five groups using analysis of variance, followed by the Newman–Keuls test for multiple comparisons. Fasciculation and postoperative muscle pain data were analyzed by Fisher's exact test. Onset and recovery times were analyzed by Student's unpaired *t*-test using the Bonferroni correction, when indicated.

Results

Mean weight did not vary significantly among groups (Table 1). As one might anticipate, women undergoing tubal ligation (group T-2) were significantly ($P < 0.05$) older. Mean time from delivery to operation did not vary significantly between the two tubal ligation groups. All patients in groups C-1, C-2, T-1, and T-2 achieved 100% twitch depression, although one patient in group C-3 achieved only 98% twitch depression. All patients were easily intubated and no patient experienced muscle weakness from *d*-tubocurarine pretreatment.

There were no statistically significant differences in incidence of grade 2 fasciculations or postoperative muscle pain between pretreated and nonpretreated cesarean section or tubal ligation patients (Table 2). Overall, grade 2 fasciculations were seen in 6.7% of pretreated patients (two of 30) and in 8.9% of nonpretreated patients (four of 45). Incidence of postoperative muscle pain for all groups was 13%.

In the cesarean section patients, mean times to 100% twitch depression were 1.38 ± 0.45 min, 1.11 ± 0.51 min, and 1.09 ± 0.33 min for groups C-1, C-2, and C-3, respectively, which did not differ significantly (Table 3). In the tubal ligation patients, mean times to 100% twitch depression were 1.30 ± 0.42 min and 1.28 ± 0.42 min for groups T-1 and T-2, respectively, which did not differ significantly.

Mean time to 50% recovery for group C-2 was 9.72 ± 3.16 min, which was significantly longer than for groups C-1 and C-3. Mean time to 50% recovery for group T-2 was 8.83 ± 2.00 min, which was significantly longer than for group T-1.

Discussion

In nonpregnant surgical patients, Cullen (7), Manchikanti (14), and Blitt et al. (15) reported the incidence of vigorous fasciculations in response to succinylcholine (1 mg/kg) to be 70–100%. In contrast, Crawford (2) and Warren and Ostheimer (16) reported that in their obstetric patients, fasciculations, if present, were almost always minor. In a study by Datta et al. (9) the incidence of grade 2 fasciculations was 28% in patients during their first trimester of pregnancy and 68% in a nonpregnant control group. The low incidence of grade 2 fasciculations in nonpretreated patients in our study (8.9%) is consistent with these latter findings. Our study also found that pretreatment with 0.05 mg/kg of *d*-tubocurarine did not significantly reduce the likelihood of fasciculations.

Datta et al. (9) found postoperative muscle pain in only 20% of first trimester patients compared with 42% in a nonpregnant control group. Thind and Bryson (8) reported muscle pain in 7.5% of patients undergoing cesarean section and in 30% of the nonpregnant control group. Crawford (2) reported a 9% incidence of muscle pain in over 7000 parturients. The low incidence of postoperative muscle pain in our study is consistent with these reports.

In nonpregnant patients, pretreatment with a low dose of nondepolarizing muscle relaxant reduces the incidence of postoperative muscle pain (17), but Bry-

Table 3. Times to Onset of and 50% Recovery from Neuromuscular Blockade

	d-Tubocurarine pretreatment (0.05 mg/kg)	Succinylcholine (mg/kg)	Time to 100% twitch depression (min)	Time to 50% recovery (min)
Cesarean section				
C-1	Yes	1.5	1.38 ± 0.45	7.25 ± 1.79
C-2	No	1.0	1.11 ± 0.51	9.72 ± 3.16[a]
C-3[b]	No	0.7	1.09 ± 0.33	7.19 ± 2.72
Tubal ligation				
T-1	Yes	1.5	1.30 ± 0.42	6.84 ± 1.64
T-2	No	1.0	1.28 ± 0.42	8.83 ± 2.00[c]

Values are means ± SD; n = 15 for all groups.
[a]Varies significantly ($P < 0.025$) from groups C-1 and C-3.
[b]Data for onset time has been omitted for the one patient with only 98% twitch depression. Data for 50% recovery has been omitted for one patient who was not allowed to return to 50% recovery of twitch height for surgical reasons.
[c]Varies significantly ($P < 0.01$) from group T-1.

son and Ormston (11), in the only study involving obstetric patients, found that pretreatment with 20 mg of gallamine failed to lower the incidence of postoperative muscle pain. We found that pretreatment with *d*-tubocurarine also did not significantly reduce the incidence of postoperative muscle pain in our obstetric patients.

A number of theories have been advanced to explain the low incidences of fasciculations and postoperative muscle pain in pregnancy. Crawford (10) reasoned that it might be related to the higher concentrations of progesterone in the tissues during pregnancy, which possibly act upon skeletal muscle membranes. Datta et al. (9) felt that this low incidence might be explained by the greater dilution of the bolus of succinylcholine in plasma-expanded parturients, which resulted in a lesser amount of the drug reaching the neuromuscular junction. Marx and Bassel (1) claimed that the parturients' "increased body water content serves to reduce muscle tension." Thind and Bryson (8) suggested that "the high estrogen concentration at term renders the extrafusal and intrafusal fibers in striated muscle more pliable so that less mechanical damage to the muscle spindle occurs after succinylcholine." There are currently no data to support or refute any of these theories. Low incidences of muscle pain and fasciculations are also found in small children (18), but why this is true and how it might relate to pregnant women is unknown.

Cullen (7) reported a significant delay in onset time for succinylcholine-induced neuromuscular blockade in patients pretreated with *d*-tubocurarine, but three other studies (4,15,20) failed to show that pretreatment affects the onset of neuromuscular blockade. However, the number of subjects in each of these studies was small and Cullen did not measure twitch tension. Our study results, based on a larger sample size and measurement of twitch tension, support the contention that pretreatment does not alter the onset time of neuromuscular blockade.

In a study using dosage regimens identical to ours, Blitt et al. (15) found a trend, although not statistically significant, towards a longer recovery time in the nonpretreated group compared with the pretreated group. Cullen's study (7) revealed a similar trend that likewise did not reach statistical significance. In both the cesarean section and tubal ligation groups, our study shows a significant delay in 50% recovery time from succinylcholine-induced neuromuscular blockade in nonpretreated patients who received 1 mg/kg of succinylcholine (groups C-2 and T-2) compared with pretreated patients. This 2–2.5-min longer recovery time in nonpretreated groups may be clinically significant in the case of a failed endotracheal intubation when the patient must be awakened.

In the studies of Cullen (7), Blitt et al. (15), and in our study, succinylcholine dosage was increased 50% when *d*-tubocurarine was used for pretreatment. Freund and Rubin (5) increased succinylcholine dosage by 70% for the pretreated group and found the 50% recovery time to be similar between pretreated and nonpretreated groups. Perhaps if we had used 1.7 mg/kg (70% increase) of succinylcholine in the pretreated groups instead of 1.5 mg/kg, recovery times would have increased and equalled nonpretreatment values. Alternatively, reducing succinylcholine dosage from 1 mg/kg in nonpretreated patients might decrease recovery time towards pretreatment values. For this reason, we studied the additional 15 patients (group C-3) who were undergoing cesarean section with a reduced dosage of succinylcholine (0.7 mg/kg) and no pretreatment. The time to 50% recovery for this group was similar to the pretreated cesarean group (C-1) (Table 3). Hence, it is apparent that both time

to onset and time to 50% recovery can be similar in pretreated and nonpretreated patients if succinylcholine dosage is adjusted accordingly.

In conclusion, incidences of fasciculations and muscle pain and times to onset and recovery are similar in obstetric patients given succinylcholine, whether pretreated with *d*-tubocurarine or not, if the appropriate dosage of succinylcholine is used. Although there appears to be no benefit from pretreatment with *d*-tubocurarine, the study did not reveal any particular harm resulting from its use.

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Nitrous Oxide Does Not Increase the Incidence of Nausea and Vomiting after Isoflurane Anesthesia

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KORTTILA K, HOVORKA J, ERKOLA O. Nitrous oxide does not increase the incidence of nausea and vomiting after isoflurane anesthesia. Anesth Analg 1987;66:761–5.

A total of 110 patients undergoing elective abdominal hysterectomy were anesthetized in random order with either isoflurane in nitrous oxide and oxygen or isoflurane in air and oxygen. Fentanyl was used as an adjunct to isoflurane in all patients, 0.05 mg every 45 min. No difference was found between the two anesthetic techniques in the incidence of nausea, vomiting, or both during the first 24 hr after operation. The overall incidence was 62 and 67% for air-O_2 and N_2O-O_2 groups, respectively. Patients who had had nausea or vomiting after previous anesthetics had nausea or vomiting significantly more frequently than patients who did not. It is concluded that nitrous oxide does not contribute to the occurrence of nausea or vomiting after isoflurane anesthesia for gynecologic laparotomies.

Key Words: ANESTHETICS, GASES—nitrous oxide. ANESTHETICS, VOLATILE—isoflurane. VOMITING—postoperative.

The problem of postoperative nausea and vomiting, especially in female patients, continues despite advances in the techniques used in general anesthesia (1–3). We have conducted a series of studies in an attempt to decrease the incidence of postoperative nausea and vomiting, but without complete success (2,4–6).

It has been postulated that the administration of nitrous oxide is associated with a high incidence of postoperative nausea and vomiting (7). To the best of our knowledge, however, no properly controlled studies have been carried out to prove this.

The aim of the present study was to determine whether and to what extent nitrous oxide contributes to the occurrence of nausea and vomiting after isoflurane anesthesia. The incidence of nausea and vomiting after general anesthesia with isoflurane–air–oxygen was compared with that after isoflurane–nitrous oxide–oxygen anesthesia. Furthermore, we wanted to determine whether a history of motion sickness or a history of emesis after previous anesthetics was associated with an increased incidence of nausea and vomiting in the present study.

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Methods

Trial Design

A total of 110 patients scheduled for abdominal hysterectomy were studied. The study protocol was accepted by the institutional ethical committee, and informed consent for the study was obtained from each patient. Only patients in ASA group I or II and between the ages of 35 and 55 were studied. Patients were randomized, according to their date of birth, to receive either nitrous oxide or air. At the end of the trial, the randomization was carried out using sealed envelopes, to provide equal numbers of patients in both groups. The person recording nausea or vomiting was not aware of the type of anesthesia used.

The patients were premedicated with meperidine 1 mg/kg 40–60 min before anesthesia. After the insertion of an IV cannula and the start of IV infusion (Ringer's solution), 1.5 mg of alcuronium chloride, 0.2 mg of glycopyrrolate, and 0.1 mg of fentanyl were administered IV.

Anesthesia was induced 2 min later, using 4 mg/kg thiopental. Oral tracheal intubation was facilitated with 1.5 mg/kg of succinylcholine IV and anesthesia was maintained with either isoflurane (Forane®, Abbott) in nitrous oxide and oxygen (30%) or with isoflurane in air and oxygen (30%) administered in a semiopen or semiclosed system. The initial inspired concentration of isoflurane was 1% for those given nitrous oxide and 1.5% for those not given nitrous oxide. Thereafter, isoflurane was administered according to clin-

Table 1. Characteristics of the Test Groups (Mean ± SD)

	Isoflurane–Air–O_2	Isoflurane–N_2O–O_2
Number of patients	55	55
Age (yr)	42 ± 4	43 ± 5
Weight (kg)	66 ± 10	66 ± 12
Height (cm)	165 ± 5	163 ± 6
History of motion sickness (number of patients)	6	13
Nausea or vomiting after previous anesthetics (number of patients)	21	23
Duration of anesthesia (min)	103 ± 36	102 ± 31
Average concentration of isoflurane inspired (%)	1.4 ± 0.2	1.1 ± 0.2
Alcuronium (mg)	18 ± 4	17 ± 4
Fentanyl (mg)	0.19 ± 0.04	0.18 ± 0.04
Oxycodone for postoperative pain (mg)		
In the recovery room	16 ± 6.0	15 ± 5.5
In the ward	43 ± 11	42 ± 16

ical needs; the concentration was changed if, during the surgery, the systolic blood pressure or heart rate changed more than 25% from baseline levels. Average inspired isoflurane concentrations were estimated from the anesthesia chart in both groups. Fentanyl was used as an adjunct to isoflurane anesthesia, 0.05 mg every 45 min. Alcuronium was used to maintain neuromuscular blockade with 20–25% of the twitch response to nerve stimulation being maintained (8). End-tidal CO_2 was measured continuously with a capnometer and maintained at 5.5%. Inspired and end-tidal concentrations of isoflurane were measured with an anesthetic agent monitor in approximately half of the patients.

At the end of anesthesia, glycopyrrolate, 0.4 mg, and neostigmine, 2.0 mg, were given IV. Oxycodone chloride, to relieve postoperative pain, was administered IV in the recovery room in 4-mg increments and thereafter IM in the ward, at a dose of 0.13 mg/kg. Droperidol (1.25 mg) was used to treat postoperative nausea and vomiting. It was administered IV in the recovery room and IM in the ward if the patient vomited or had prolonged nausea.

Assessment of Nausea, Retching, and Vomiting

Nausea was defined as a wholly subjective sensation on the part of the patient. For our purposes, the feature that distinguished between a patient retching or vomiting was whether the expulsive efforts of the patients produced even a smallest amount of stomach contents. If it did not, it was classified as retching.

The incidence of nausea, retching, and vomiting in five intervals was determined during the first 24 hr after operation: from 0 to 2 hrs, 2 to 6, 6 to 12, 12 to 18, and 18 to 24 hrs, as in our previous studies (2–5). At the end of each interval, a trained nurse registered whether retching or vomiting had occurred and asked the patient whether the patient felt nauseated. The results were scored, as in our previous studies, in a manner similar to that of Bellville et al. (9): none, nausea, retching, vomiting. If a patient had nausea, retching, and vomiting, she was was listed as having had vomiting.

Statistics

Student's t-test was used for comparisons of the patients' characteristics and of the types of anesthesia. The χ^2-test was used to compare the incidence of nausea, retching, and vomiting; for any comparison, data for each patient was recorded only in one cell of the data table. Thirteen patients were excluded from the comparison in Fig. 3 because they had not had previous anesthetics.

Results

The principal finding was that omission of nitrous oxide did not decrease the incidence of nausea or vomiting. The two groups were similarly constituted (Table 1): the duration of anesthesia, the amounts of alcuronium required for muscle relaxation, and the doses of intraoperative fentanyl and postoperative oxycodone were similar. The average inspired concentration (mean ± SD) of isoflurane was 1.1 ± 0.2% for those given nitrous oxide and 1.4 ± 0.2% for those not given nitrous oxide (Table 1).

Figure 1 shows that the incidence of nausea, retching, and vomiting during the first 24 hr postoperatively was similar in both groups. Nausea, retching, or vomiting were experienced by 62–67% of patients, regardless of the anesthetic technique used. Thirty-three percent of patients had nausea in both groups,

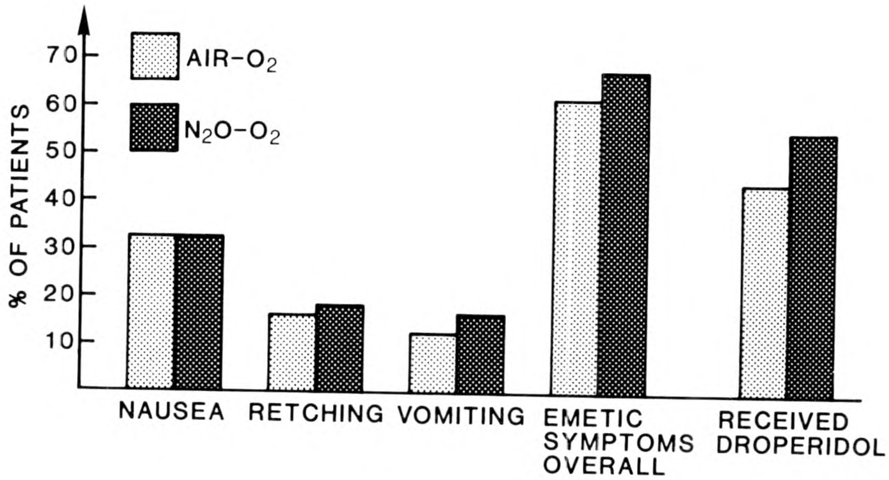

Figure 1. Incidence of postoperative nausea, retching, and vomiting and percentage of patients given droperidol as an antiemetic after isoflurane–air–oxygen (air–O_2) or isoflurane–nitrous oxide–oxygen (N_2O–O_2) anesthesia for abdominal hysterectomy.

and 13 and 16% of patients vomited in the isoflurane–air–O_2 group and the isoflurane–N_2O–O_2 group, respectively. Approximately half of the patients in both groups were given droperidol for nausea, retching, or vomiting (Fig. 1).

Figure 2 shows the incidence of emesis at different times after anesthesia. There was no difference between the two anesthetic techniques in the incidence of nausea and vomiting during any time interval studied. Nausea or vomiting were most frequent 6–12 hr after anesthesia (Fig. 2).

Significantly ($P < 0.01$) more patients had emesis if they had experienced nausea or had vomited after previous anesthetics than did patients who reported no nausea or vomiting after previous anesthetics (Fig. 3). A history of motion sickness was also associated with a high incidence of nausea and vomiting after anesthesia, but this incidence was not statistically significant when compared with patients without a history of motion sickness. Of the 19 patients who had a history of motion sickness, 16 developed nausea or vomiting in the present study, which was the case in 53 of the 89 patients who did not have a history of motion sickness (χ^2-test between the groups: $\chi^2 = 6.67$; $P = 0.08$).

Discussion

In the present investigation, the omission of nitrous oxide from an anesthetic technique did not decrease nausea or vomiting after anesthesia. The trial design and scoring system used for nausea and vomiting in this investigation have been used by us before and have proved useful and sensitive in evaluating the postoperative antiemetic efficacy of drugs after general anesthesia (2,4–6,9). Comparison of the findings between the two groups in the present investigation is justified, because the variables that most affect the incidence of nausea and vomiting (i.e., age, sex, type and duration of operation, history of nausea or vomiting after previous anesthetics, history of motion sickness, and amounts of narcotic given) were similar in these groups. Although the administration of narcotic analgesics may cause nausea and vomiting, we chose to use meperidine for preanesthetic medication and small doses of fentanyl to supplement isoflurane anesthesia, as pain after operation has also been implicated as a major cause of postoperative nausea (10).

The overall incidence of nausea and vomiting in this study (62 and 67% with air–O_2 and N_2O–O_2 groups, respectively) is similar to the figures reported in our previous studies (2,4,5). However, the patients in this study given isoflurane had less vomiting (13–16% vomited) than did patients who in our previous studies were given enflurane (41–64% vomited) or fentanyl–nitrous oxide–oxygen anesthesia (41% vomited) when no prophylactically administered antiemetic drugs were given (2,4,5). Controlled studies should be conducted to determine whether the incidence of nausea and vomiting after isoflurane anesthesia is less than after enflurane anesthesia or balanced anesthetic techniques.

Knapp and Beecher (11) reported in the 1950s that 78% of female patients anesthetized with ether in nitrous oxide and oxygen had nausea or vomited. Bonica et al. (12) reported that the incidence of nausea and vomiting in gynecologic patients was 41% when anesthetics other than ether was used. It is difficult to compare the findings in the earlier studies with the present data because in the earlier studies, the anesthetic techniques were not controlled, and a variety of surgical procedures were included.

Eger (7) has postulated that the administration of nitrous oxide increases the incidence of postoperative

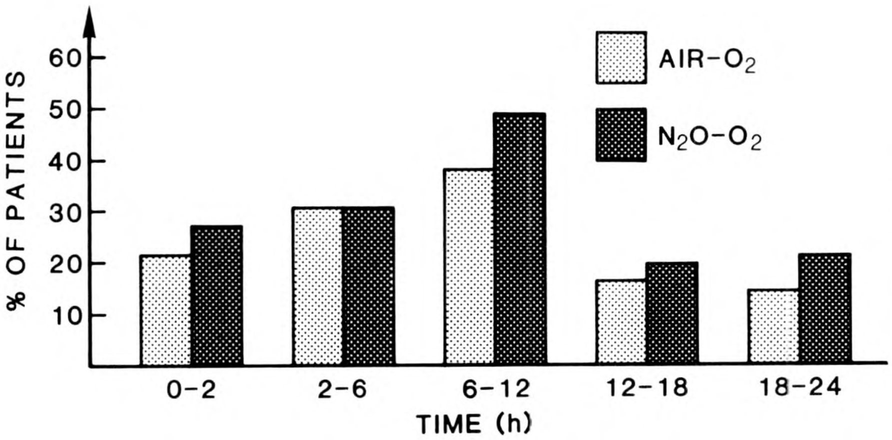

Figure 2. Incidence of postoperative emesis (nausea, retching, or vomiting) during different intervals after isoflurane–air–oxygen (air–O_2) or isoflurane–nitrous oxide–oxygen (N_2O–O_2) anesthesia for abdominal hysterectomy.

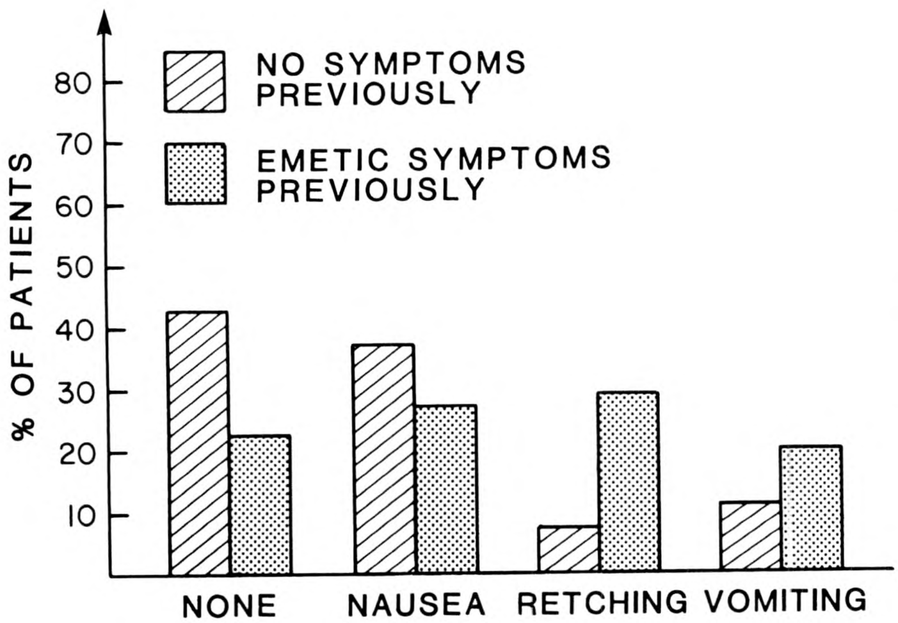

Figure 3. The incidence of postoperative nausea, retching, and vomiting in patients undergoing abdominal hysterectomy under general anesthesia. Comparisons are made between patients with nausea or vomiting after previous anesthetics (n = 44) and those without nausea or vomiting after previous anesthetics (n = 53). χ^2-test between groups: $\chi^2(df = 3) = 11.75$; $P < 0.01$.

nausea and vomiting. Alexander et al. (13) have reported that the incidence of nausea and vomiting is greater (61%) in patients anesthetized with fentanyl and nitrous oxide in oxygen than in patients anesthetized with isoflurane in oxygen with (30%) or without (25%) fentanyl for pelvic laparoscopy. Nitrous oxide was not, however, the only variable changed in their patients. Similarly, Lonie and Harper (14) reported that significantly fewer (17 vs 49%) patients vomited when nitrous oxide was omitted from enflurane anesthesia for gynecologic laparoscopy. Recently Muir et al. (15) found no association between the use of nitrous oxide and postoperative nausea and vomiting in patients undergoing a variety of surgical procedures under enflurane or isoflurane anesthesia with or without nitrous oxide. In the present study, where the groups differed only with respect to administration of nitrous oxide, the incidence of emetic symptoms did not depend on the administration of nitrous oxide. (In addition, a higher concentration of isoflurane was given to patients not receiving nitrous oxide compared with those who received nitrous oxide.)

Our finding that patients are more likely to have postoperative nausea and vomiting if they have had nausea or vomiting after previous anesthetization confirms what was already thought to be true. However, the ability of patients to remember nausea and vomiting following previous anesthetics is limited, which make statistical comparisons weak.

Nitrous oxide is used almost routinely in most general anesthetics administered today. As the omission of nitrous oxide from the anesthetic technique used in this study did not decrease the incidence of emetic

symptoms postoperatively, the use of nitrous oxide need not be avoided in women undergoing gynecologic laparotomies, even in the patients who are most prone to vomiting after anesthesia.

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Comparison of Halothane and Isoflurane for Rapid Anesthetic Induction

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LOPER K, REITAN J, BENNETT H, BENTHUYSEN J, SNOOK L. Comparison of halothane and isoflurane for rapid anesthetic induction. Anesth Analg 1987;66:766–8.

To study the hypothesis that isoflurane will induce anesthesia faster than halothane when given by a single vital capacity breath technique, we studied 20 ASA I and II adults who breathed approximately 4.5 MAC equivalents of either vapor. The patients, randomly assigned to receive either agent, were fully preoxygenated and monitored for cardiovascular, respiratory, and EEG parameters. All subjects were premedicated with 5 μg/kg fentanyl IV 5 min before induction. Time to loss of consciousness was significantly longer with halothane than with isoflurane (86 ± 4 vs 38 ± 2 sec, respectively) although there were no clinically remarkable differences in cardiovascular or respiratory variables. Patients given halothane had a greater excitatory phase on EEG, whereas those given isoflurane had low frequency predominance. Overall rapid inhalation induction was well-received by all patients and was significantly faster with isoflurane.

Key Words: ANESTHETICS, VOLATILE—halothane, isoflurane. INDUCTIONS, ANESTHESIA—halothane, isoflurane.

In 1954, Bourne reported on the use of cyclopropane for outpatient dental surgery, using a novel technique that included having patients hold a single vital capacity breath (VCB) of the inhalation agent until unconsciousness ensued (1). At the time his work was published, inhalational induction of anesthesia had been widely abandoned in favor of intravenous drugs. The unpleasant experiences associated with the excitatory phase of diethyl ether were thereby avoided. Thus cyclopropane offered an alternative: loss of consciousness was rapid, arterial blood pressure was well maintained, and emergence was without delay. Unfortunately the explosive risk of cyclopropane forced its discontinuation; rapid induction again fell into the domain of intravenous agents.

Ruffle et al. reported on the use of Bourne's technique for inhalation induction utilizing 4% halothane in oxygen wherein the onset of unconsciousness was achieved in less than 3.5 min in 15 of 16 patients (2). Mean induction time was not reported. More recently, Wilton and Thomas demonstrated that with 4% halothane in a 2:1 mixture of N_2O and O_2, unconsciousness was attained with a mean induction time of 83 sec (3).

The blood: gas solubility of isoflurane is less than that of halothane (4). Hence isoflurane would be expected to produce a more rapid anesthetic induction than halothane. The purpose of our study was to compare the use of these two inhalation anesthetics during rapid inhalation induction of anesthesia.

Methods

The study was approved by the University Human Research Committee, and informed consent was obtained from each patient. Twenty ASA I and II adult patients undergoing elective surgery were randomly designated to receive either 3.5% halothane or 5% isoflurane. These concentrations represent approximately 4.5 MAC for each agent. Monitoring included a continuous electrocardiogram (lead II), an automatic noninvasive blood pressure recorder (Sentron), pulse oximetry (Nellcor), and capnometry (Datex).

Additionally, two-channel monopolar electroencephalogram (EEG) recordings were obtained utiliz-

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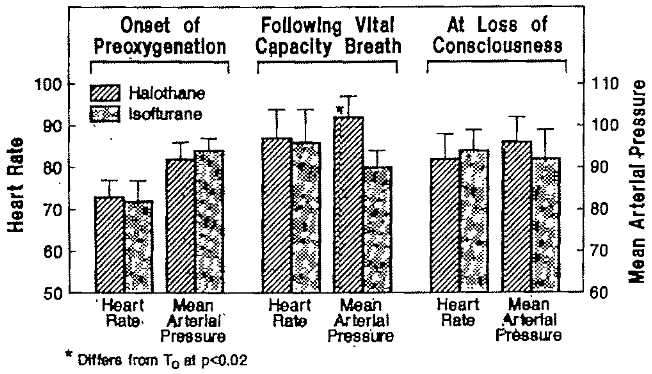

Figure 1. Cardiovascular values during inhalation induction with halothane and isoflurane. Heart rate (beats/min) and mean arterial pressure (mm Hg) were recorded 1) during the preoxygenation control, 2) immediately after the vital capacity breath (VCB), and 3) at the time of loss of consciousness. Values expressed in the bar graphs are mean ± 1 SEM. With the VCB, mean arterial pressure rose significantly in the halothane group.

ing a compressed spectral array and power-band numerical printout (Neurotrac, Interspec Medical). The power bands were displayed numerically as picowatts of EEG power for both left and right hemispheres with bilateral frontal-mastoid lead placement and a frontalis ground lead. Since artifact is associated with breath holding and endotracheal intubation, data were analyzed offline during artifact free periods: 1) just prior to the first VCB and 2) following intubation. Baseline numerical values for each channel were compared with values after intubation for each frequency band and a ratio of the values before and after induction was computed.

Patients were premedicated with glycopyrrolate, 0.2 mg, intramuscularly 15 min before anesthesia. Using a McGill breathing circuit, the subjects were preoxygenated with 100% O_2 at a flow of 12 L/min for 6 min. To suppress the cough reflex, fentanyl, 5 μg/kg, was administered intravenously during the first 2 min of preoxygenation. The selected inhalation agent in oxygen was then delivered from an Ohio Modulus anesthestic machine fitted with Ohio calibrated vaporizers and a circle system with an approximate volume of 8 L. In each individual experiment, the Ohio system was flushed for 4 min at 8 L/min oxygen flow with the vaporizer set at the desired concentration of the assigned agent. The excess gas was vented through the pop-off valve and breathing hoses.

Following preoxygenation, the patients were instructed to breathe out to residual volume and hold their breath at residual volume while the McGill circuit was replaced by the preprimed circle system. They were then instructed to take a VCB and attempt to hold this breath as long as they could, preferably until loss of consciousness (LOC) ensued. Following this initial VCB, patients were allowed to resume spontaneous respiration. LOC was defined as the loss of both lid reflex and response to verbal command.

Table 1. Mean Ratios of EEG Power Changes (and Range) Comparing the Baseline Preoxygenation Values with Those Following Intubation

EEG band	Halothane	Isoflurane
δ	1.71 (0.14–10.6)	2.07 (0.68–20.0)
θ	1.05 (0.18–3.2)	1.86 (0.45–6.5)
α	0.95 (0.32–7.6)	5.21 (1.1–9.1)
β	2.11 (0.22–6.5)	1.84 (0.44–3.1)
Total	1.59 (0.44–3.1)	2.06 (0.95–3.8)

Following LOC, succinylcholine was administered to facilitate intubation. Maintenance of anesthesia was achieved by continuing the preselected agent at a level titrated to the patient's anesthetic requirement.

An independent observer recorded the heart rate, mean arterial pressure, arterial oxygen saturation, end-tidal CO_2, the total number of breaths, including the first vital capacity breath, and the time required to attain LOC. Each vaporizer was calibrated with an Emma gas analyzer and actual delivered concentrations of their respective inhalation agents were verified by sham calibration trials. From the four anesthesia machines used in this study, halothane concentration was 3.52 ± 0.02% and isoflurane was 5.00 ± 0.03%.

Statistical analysis on the data was performed using Student's t-tests with $P < 0.05$ accepted as statistically significant. All values are expressed as means ± SEM.

Results

The mean time for induction of anesthesia following the first VCB was significantly more rapid with isoflurane than with halothane (38 ± 2 sec and 86 ± 4 sec, respectively). Patients given halothane took an average of 4.9 ± 0.3 total breaths before LOC, significantly greater than the 2.2 ± 0.1 breaths with isoflurane. Fentanyl effectively blocked the cough reflex in all patients.

The cardiovascular values are presented in Fig. 1. During induction with isoflurane there were no significant changes in either HR or MAP. There was similar stability with halothane, the slight increase in MAP following the VCB being statistically but not clinically significant.

There were no significant differences between halothane and isoflurane with respect to arterial oxygen saturation (99 ± 0.6% vs 100 ± 0.2%, respec-

tively) or end-tidal CO_2 (44 ± 2 mm Hg vs 45 ± 2 mm Hg, respectively) at LOC. Neither were there significant differences with respect to age, sex, weight, or smoking history.

Left and right channel EEG findings were not significantly different and were combined in the ratio changes presented in Table 1. Halothane increased power in the higher frequency ranges whereas isoflurane produced a pattern centered in the middle frequencies.

A survey of all patients on the following day revealed that the experience was viewed positively and that, without exception, all would accept the technique again. There was no incidence of perioperative emesis in any patient. Interestingly, in neither group was there recollection of induction following their VCB of the volatile agent.

Discussion

This study demonstrates that inhalational induction of anesthesia with either isoflurane or halothane is a safe and effective technique in the cooperative adult patient. With inhalation anesthesia the steady-state concentration of the agent in the brain correlates well with the alveolar concentration (4). However, during induction the rapid uptake of the volatile agent by blood will lower the alveolar concentration. With the more soluble agents this will slow induction. Consequently, the inspired concentration of an agent for induction must be considerably higher than its MAC. Thus to achieve a rapid inhalation induction, high concentrations (approximately 4.5 MAC) of the volatile agents were used. Further, by having the patient exhale to residual volume and then inhale to vital capacity, the delivery of volatile agent to the alveoli in the first breath was at a clinical maximum.

Isoflurane produced a more rapid induction than halothane. Our finding of a mean induction time of 86 sec for halothane is in agreement with previously reported data (2,3). Given the lower blood : gas solubility of isoflurane, it is not surprising that it produced a significantly more rapid induction with a mean induction time of 38 sec. Cardiovascular stability with both agents was notable despite the mild Valsalva maneuver that accompanies a VCB at the high anesthetic concentrations used. The 5-μg/kg dose of fentanyl successfully attenuated the cough reflex in our subjects to the point of accepting the isoflurane induction. Certainly the narcotic accelerated the induction time, but probably to the same degree for both isoflurane and halothane.

The EEG findings were consistent with an activation pattern after halothane induction. Patients with an increase in high-frequency power might be aroused or more responsive to surgical stimulation. Possibly the longer induction time with halothane may predispose the patient to a prolonged excitement phase, with consequent EEG activation.

Our patients found this type of rapid inhalation induction of anesthesia pleasant. That patients had no recollection of events past their VCB indicates that amnesia preceded loss of unconsciousness. Hypoxia does not occur with this technique as the patient is well preoxygenated, nor does the $ETCO_2$ increase markedly with the brief period of apnea.

We conclude that isoflurane offers an alternative to halothane for rapid inhalation anesthetic induction in the cooperative adult patient. This study involved healthy patients, and we suspect that individuals in poor health or with diminished lung function would be inappropriate candidates for this type of induction. The low blood : gas solubility of isoflurane allows rapid induction with notable cardiovascular stability.

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Toxicity of Sevoflurane in Rats

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STRUM DP, EGER EI II, JOHNSON BH, STEFFEY EP, FERRELL LD. Toxicity of sevoflurane in rats. Anesth Analg 1987;66:769–73.

Sevoflurane, an experimental potent volatile anesthetic with a low blood/gas partition coefficient, degrades in the presence of soda lime to products the toxicity of which is unknown. We tested whether toxic products were produced by the passage of sevoflurane through soda lime, and a comparison was made of the toxicity of sevoflurane passed through soda lime with the toxicity of other potent volatile anesthetics in current clinical use. Halothane, isoflurane, sevoflurane (all in 1-MAC concentrations), or no anesthetic (control) were passed through soda lime for 4 hr with 12, 14, or 100% oxygen to groups of rats with hepatic microsomal enzyme induction. Separate groups of 12–13 rats were given 1 MAC of sevoflurane that had not passed through soda lime and either 14 or 100% oxygen. Sevoflurane was no more toxic than isoflurane and both of these anesthetics were less toxic than halothane. Soda lime was not a factor in any toxicity produced. Hepatic injury with all agents varied inversely with the oxygen concentration administered during anesthesia.

Key Words: ANESTHETICS, VOLATILE—halothane, isoflurane, sevoflurane. TOXICITY—sevoflurane. LIVER—hepatotoxicity.

Sevoflurane is a rapid-acting, potent, inhaled anesthetic (1,2) having rapid uptake and elimination due to a low blood/gas partition coefficient. Interest in sevoflurane has increased with the recent emphasis on outpatient surgery because recovery from this anesthetic is rapid.

To be useful clinically, an anesthetic must be devoid of toxicity. Sevoflurane has been reported to be unstable on exposure to soda lime, the degradation amounting, however, to only a few percent in 3 hr (1). In contrast, we observed a 1,000-fold decrement in the concentration of sevoflurane over 24 hr when we passed sevoflurane vapor through soda lime (Strum and Eger, Stability of sevoflurane in soda lime, submitted for publication). This difference in results is greater than was expected and may be due to differences in methods of study. Previous studies used liquid sevoflurane and measured the dilution of sevoflurane by degradation products; we used sevoflurane vapor (which is more relevant to clinical practice) and measured the rate of disappearance of the parent compound.

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The degradation of halothane by soda lime is known to produce toxic products (3), and the same may be true of sevoflurane. One study suggested that administration of sevoflurane in the presence of soda lime might injure the liver and kidney, but injury was considered more likely related to hyperthermia and a thermoregulatory defect rather than to a specific chemical toxicity (4). In addition, an examination for possible hepatic, renal, and pulmonary injury was not done in that the lung was not examined and hyperthermia confounded the results for liver and kidney (both of which did show injury). The investigators noted that other, currently accepted anesthetics appeared to produce the same effect.

Studies by Wallin et al. (1) and by Holaday and Smith (2) have not shown hepatic injury after sevoflurane given in the presence of soda lime. However, the study by Holaday and Smith (2) exposed animals to sevoflurane for only 1 hr at 1 MAC, and neither study used phenobarbital-pretreated animals or imposed a hypoxic or thermal stress. The concurrent application of a stress and anesthesia may be important to the development of hepatic injury. Hepatic injury may not result in the unstressed, anesthetized rat (or human). In addition to products of biodegradation or breakdown by soda lime, initiation of toxic responses may require an increase in hepatic oxygen consumption (hyperthermia, phenobarbital pretreatment) or a decrease in oxygen availability (hypoxia,

Table 1. Hepatic Injury Associated with Hypoxia, Anesthetic Agent, and Use of Soda Lime

				Rats with injury		% of Lobule with injury		% of Lobule necrosed	
Agent	O_2%	Soda lime	*n*	Number	%	Mean	SD	Mean	SD
Ctl	12	yes	22	13/22	57.1	11.3	18.8	4.9	12.8
Iso	12	yes	26	23/26	88.5[a]	23.9	19.4[a]	13.1	15.5
Halo	12	yes	27	27/27	100.0[a]	30.6	12.8[a]	13.3	13.9
Sevo	12	yes	38	33/38	86.8[a]	21.5	13.7[b]	9.2	8.5
Ctl	14	yes	38	4/38	10.5	0.8	2.8	0.1	0.2
Iso	14	yes	14	8/14	57.1[a]	3.8	6.3[b]	0.9	1.9[b]
Halo	14	yes	23	22/23	95.7[a]	20.7	18.4[a]	10.2	11.5[a]
Sevo	14	yes	26	11/26	42.3[a,b]	6.5	11.6[b]	2.7	5.3[b]
Sevo	14	no	12	6/12	50.0[a,b]	6.7	12.4[b]	3.6	8.6
Ctl	100	yes	25	0/25	0.0	0.0	0.0	0.0	0.0
Sevo	100	yes	26	0/26	0.0	0.0	0.0	0.0	0.0
Sevo	100	no	13	0/13	0.0	0.0	0.0	0.0	0.0

Abbreviations: Ctl, control; Iso, isoflurane; Halo, halothane; Sevo, sevoflurane.
[a]Significantly different ($P < 0.05$ with Bonferroni correction) from control.
[b]Significantly different from results for halothane ($P < 0.05$).

decreased hepatic blood flow consequent to anesthetic administration), or both.

The breakdown of sevoflurane in basic environments (soda lime) suggests that certain other tissues are at risk of injury. If breakdown to reactive products results from the action of base on sevoflurane, then tissues such as the pancreas or duodenum may be sites of greater breakdown and injury because of their relatively high pH. To investigate the toxicity of sevoflurane, we asked three questions: 1) Is sevoflurane toxic when administered in the presence of soda lime? 2) Does the presence of hypoxia (and enzyme induction) exaggerate this toxicity? and 3) Is sevoflurane more or less toxic than isoflurane or halothane?

Methods

With approval from our Committee on Animal Research, we obtained male, specific pathogen free, Sprague-Dawley rats (Bantin and Kingman) aged 2–3 months and weighing 250–350 g. A rat model was chosen because it has been suggested that these animals are more sensitive to organ injury from sevoflurane than are mice or guinea pigs (4). Groups comprising 10–14 rats each were studied. To induce hepatic microsomal enzymes, the rats were pretreated for 5 days by adding phenobarbital, 1 mg/ml, to their drinking water. Each rat was weighed at the start and end of a 5-day period of phenobarbital pretreatment. The volume of phenobarbital solution consumed by each rat was measured, and rats consuming <50 mg phenobarbital per 5-day period were excluded from study. Phenobarbital was discontinued for 24 hr before administration of anesthetic.

Each rat from each group was placed in an individual exposure chamber and, excepting the control groups, received anesthetic at 0.9–1 MAC for 4 hr in 12, 14, or 100% oxygen (balance nitrogen). Oxygen concentration was measured with a Beckman E2 (Pauling) meter, calibrated before each study with nitrogen and 100% oxygen. The average gas flow through each chamber was 1 L/min. Rectal temperatures were measured (except in control rats in the 14% oxygen groups) and was maintained between 38 and 39°C by the application of heat (infrared lamps) or cold (ice) to individual chambers.

Concentrations of anesthetics were measured by infrared analysis (Beckman LB2) and gas chromatography. The chromatograph column consisted of 10% S.F. 96 on Chromasorb WHP, 68/80-mesh, 0.32 by 4.6 m, and maintained at 30°C. A nitrogen carrier stream flowing at 45 ml/min delivered the sample through the column to a flame ionization detector (at 200°C) supplied by hydrogen at 40 ml/min and by air at 280 ml/min. Primary volumetric standards were used to calibrate the tanks containing the anesthetics to be studied. The gas chromatograph and infrared analyzers were calibrated with gas from these secondary (tank) standards.

Anesthetics were administered from temperature-compensated vaporizers (Ohio Medical Anesthetics). A mixture of gases consisting of oxygen and 4% carbon dioxide, balance nitrogen, was directed through the vaporizer to produce an inspired concentration of

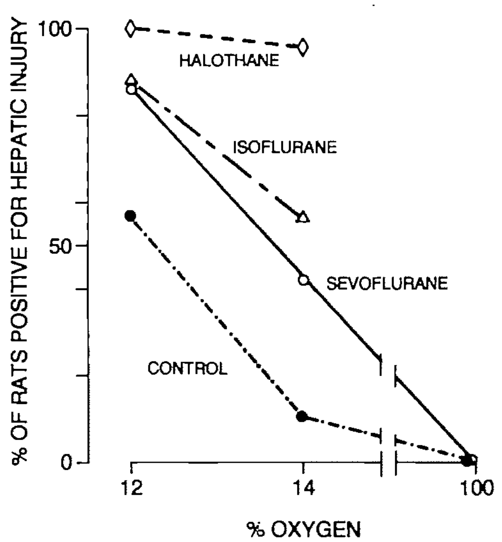

Figure 1. The percentage of rats showing hepatic injury (means) is inversely proportional to the oxygen concentration administered with anesthesia. Halothane-treated rats sustained more hepatic injury than did other groups and the control rats sustained less hepatic injury than did other groups. The hepatotoxic effects of sevoflurane and isoflurane were indistinguishable at each concentration of oxygen.

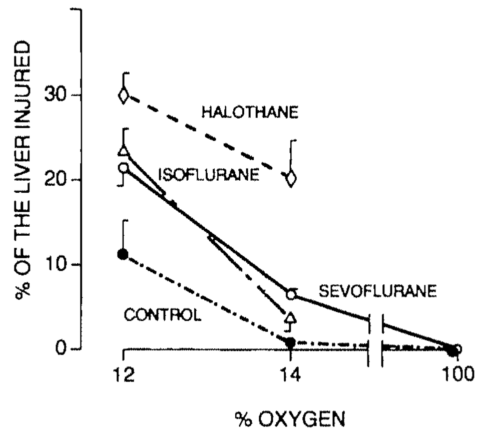

Figure 2. The percentage of hepatic tissue injured (means ± SEM) is inversely proportional to the oxygen concentration administered with anesthesia. Halothane-treated rats sustained more hepatic injury than did other groups and control rats sustained less hepatic injury than did other groups. The hepatotoxic effects of sevoflurane and isoflurane were indistinguishable at each concentration of oxygen.

oxygen without carbon dioxide of 12, 14, or 100%. Carbon dioxide levels were monitored upstream and downstream from the carbon dioxide absorber with infrared analyzers (Beckman LB2), calibrated with tank standards (Liquid Carbonic).

The anesthetic gas mixture was directed through a humidifying canister containing water and then through four standard disposable soda lime absorbers (Disp CO_2 Sorb, Dryden Corporation). The humidifier and each of the soda lime absorbers were connected in series and were maintained in a water bath at 54°C. Fresh absorbers were used and the humidifier refilled with fresh water for each group of rats. Gas concentrations in the effluent from the absorbers were analyzed to ensure that 0.9–1 MAC concentrations of anesthetic were sustained and that no carbon dioxide was delivered to the rats. Gases exiting from each rat's chamber were scavenged.

Rats were assigned to receive a specific anesthetic (or no anesthetic) at a specific oxygen concentration for a 4-hr period (Table 1). At the end of this period, the anesthetic was discontinued and the rats were given air to breathe, after which they were returned to their cages and given rat chow and pure water ad lib.

Twenty-four hours after anesthesia, the rats were killed by inhalation of carbon dioxide and were immediately necropsied. Samples of duodenum, kidney, lung, liver, and pancreas were removed and fixed in 10% buffered formalin. For each specimen, a slide was prepared and coded. All slides for a given tissue were randomized and examined by a pathologist (LDF) who was unaware of the treatment given each rat. All specimens were graded for the presence or absence of injury; hepatic specimens were also graded for the percentage of the lobule that showed swelling and for the percentage that showed necrosis. The sum of these two grades of injury was taken as the total percentage of the lobule that was injured. Pulmonary tissue was also examined for the presence of acute (≤24 hr) and chronic injury (>24 hr).

Data were analyzed using analysis of variance, Fisher's exact test, and χ^2-test. We anticipated that the toxicity of sevoflurane would be expressed by production of greater injury than that produced by isoflurane. We anticipated (at least for hepatic tissue) that at each oxygen concentration, livers from control rats would show the least injury; those from isoflurane-treated rats would show intermediate injury; and those from rats given halothane would show the most injury. Finally, we anticipated that any injury would be exaggerated by increased hypoxia.

Results

Both the percentage of liver tissue showing injury (Fig. 1) and the percentage of rats having injury to the liver (Fig. 2) varied inversely with the oxygen concentration received during anesthesia. With 100% oxygen, no rat had hepatic injury. Isoflurane and sevoflurane did not differ in the extent of hepatic injury produced at each concentration of oxygen (Fig. 1 and 2; Table 1). Hepatic injury in both these groups was

Table 2. Pulmonary Injury Score Associated with Hypoxia, Anesthetic Agent, and Use of Soda Lime

Agent	O_2%	Soda	*n*	Rats with injury		Chronic injury		Acute injury	
				Number	%	Number	%	Number	%
Ctl	12	yes	22	6/22	27.2	2/22	9.1	4/22	18.2
Iso	12	yes	26	3/26	11.5	2/26	7.7	1/26	3.8
Halo	12	yes	27	2/27	7.4	0/27	0.0	2/27	7.7
Sevo	12	yes	38	6/38	15.8	4/38	10.5	2/38	5.3
Ctl	14	yes	38	8/38	21.1	1/38	2.6	7/38	18.4
Iso	14	yes	14	0/14	00.0	0/14	0.0	0/14	0.0
Halo	14	yes	23	9/22	40.9	8/22	36.4	2/22	9.1
Sevo	14	yes	26	1/26	3.8	1/26	3.8	0/26	0.0
Sevo	14	no	12	0/12	0.0	0/12	0.0	0/12	0.0
Ctl	100	yes	25	11/25	44.0	5/25	20.0	7/25	28.0
Sevo	100	yes	26	9/26	34.6	6/26	23.1	4/26	15.4
Sevo	100	no	13	11/13	84.6	4/13	30.8	9/13	69.2

Abbreviations: Ctl, control; Iso, isoflurane; Halo, halothane; Sevo, sevoflurane.

intermediate between that sustained by rats in the halothane and in the control groups. For example, at 14% oxygen, the percentage of injury in the combined isoflurane and sevoflurane groups was significantly less than that in the halothane group ($P = 0.00005$, Fisher's exact test) and greater than that in the control group ($P = 0.00015$). The passage of sevoflurane through soda lime did not influence the extent of hepatic injury at either 14 or 100% oxygen.

Results of histologic examination of pulmonary tissue were variable. More injury occurred with the 12 and 100% concentrations of oxygen than with the intermediate concentration of 14% (Table 2). Neither sevoflurane nor the other anesthetics enhanced injury to the lung. However, rats given 100% oxygen and sevoflurane without soda lime had an incidence of acute pulmonary injury greater than that found in control rats ($P < 0.022$, Fisher's exact test) and in rats given sevoflurane that has passed through soda lime ($P < 0.0019$).

No significant differences among rats differently exposed were found for injury to the pancreas, duodenum, or kidney. No rat had evidence of duodenal injury. One rat given 12% oxygen and isoflurane and one rat given 14% oxygen and sevoflurane without soda lime had renal injury. Eight rats had evidence of peritonitis that involved the pancreas: in the rats given 14% oxygen, three given isoflurane, one given halothane, and two given sevoflurane with soda lime had such injury; in the rats given 100% oxygen, two given sevoflurane with soda lime had such injury. Peritonitis occurred more often (8 of 101) in rats in which large (3.4 mm-diameter) rectal probes were placed for temperature monitoring. One rat in which a large rectal probe had been placed had a ruptured large bowel. Peritonitis did not occur in rats in which no probe was placed or in which a smaller diameter probe (2.0 mm) was used (0 of 163). The difference between these two groups was significant ($P < 0.0005$, Fisher's exact test).

Omitted from our study were six rats that died during exposure to hypoxia. Among the rats given 14% oxygen, two control rats died. Among the rats given 12% oxygen, two rats in the sevoflurane group and one each in the isoflurane and halothane groups died during exposure to hypoxia.

Discussion

Our study addressed three questions: 1) Is sevoflurane toxic when administered with soda lime? 2) Is sevoflurane toxic when given with hypoxia (and enzyme induction)? and 3) Is sevoflurane more or less toxic under these conditions than isoflurane or halothane?

We found that the presence of soda lime sevoflurane did not increase damage to any organ at either 14 or 100% oxygen. We conclude that soda lime does not cause sevoflurane to become toxic in rats. Compared with results with no anesthetic, sevoflurane with hypoxia in the presence of (presumed) hepatic enzyme induction produced no toxic effect in any organ except the liver, and hepatic injury was inversely proportional to the administered oxygen concentration (Fig. 1 and 2; Table 1). Sevoflurane and isoflurane were statistically indistinguishable in the degree of hepatic injury they produced at each concentration of oxygen. This similarity implies that sevoflurane is no more toxic than isoflurane, which is currently the most widely used potent inhaled an-

esthetic. In contrast, halothane was more toxic than isoflurane or sevoflurane at both 12 and 14% oxygen.

Our findings are consistent with several previous observations (5,6) that all anesthetics can produce hepatic injury in enzyme-induced, hypoxic rats. However, our results differ from those obtained in previous studies (7) that failed to find hepatic injury in rats given isoflurane in 12% or 14% oxygen. Several factors explain this difference. First, the 4-hr exposure to anesthesia and degree of hypoxia used in the present study were both greater than in previous studies. Second, we maintained body temperatures at higher levels in rats during anesthesia and hypoxia (38–39°C) than did other investigators (36.5–38.5°C) (6,7). However, we note that one study (4) reported severe hepatic damage associated with sevoflurane anesthesia in rats with body temperatures exceeding 40°C. Third, we used 0.9–1 MAC rather than 0.3 MAC (6,7) to anesthetize the rats.

The conditions of our study imposed a severe stress on our rats. Evidence of this is found in the injury suffered by the liver. Evidence of severe stress also is found in deaths of rats (both experimental and control) during exposure to hypoxia. The absence of death or hepatic injury when 100% O_2 was given emphasizes the important role of hypoxia in producing hepatic injury with each anesthetic.

A curious finding was that acute and chronic pulmonary injury developed in rats given 100% oxygen, and acute pulmonary injury developed in control rats given either 12 or 14% oxygen. Acute injury was manifested by a polymorphonuclear cell infiltration in the bronchial lumen, acute pneumonia, or pulmonary edema. Chronic injury consisted of lipoid or organizing pneumonia.

Acute pulmonary injury in rats exposed to 100% oxygen may have resulted from oxygen toxicity. Aspiration during anesthesia also may have caused pulmonary injury. Pulmonary edema secondary to pulmonary hypertension may have been induced by hypoxia (that is, in the rats given 12 or 14% oxygen). Alternatively, the acute pulmonary injury may have been unrelated to the experiment itself. Such injury ocurred predominantly in rats who were housed together in single cages, and who had arrived together for the middle third of the study, which included the exposures to 100% oxygen. An appreciable but decreasing incidence of acute injury occurred in rats arriving subsequently and exposed to 12% oxygen. Most of this injury was present in the middle and (to a lesser extent) last third of the rats studied. These observations suggest that an infection appeared in our rats and spread to others in the colony at about the midpoint of our study. If an infection was present, it did not appear to compromise the results for the other tissues studied. We could not demonstrate a relationship between acute pulmonary injury and hepatic injury in any treatment group or between any of the combined groups. The lowest probability obtained for each of 16 comparisons was $P = 0.1425$ (Fisher's exact test).

Another interesting pulmonary finding appeared in the rats given sevoflurane in the presence of 100% oxygen. The absence of soda lime was associated with a significantly higher incidence of overall ($P < 0.005$) or acute ($P < 0.02$) pulmonary injury (Fisher's exact test). One possible explanation for this finding is that soda lime absorbs a toxic product, perhaps a contaminant of the sevoflurane. However, we found only minute traces of compounds other than sevoflurane in the chromatographic patterns of the gases that did not pass through soda lime (the area of these compounds was <0.1% of the area of the sevoflurane). An additional point of evidence against the toxic-contaminant thesis is that rats given sevoflurane with 14% oxygen and no soda lime had no pulmonary injury. As indicated above, we believe that the development of an acute infection at the midpoint of the study explains the injury in the rats given 100% oxygen. The absence of infection also explains the absence of injury in the rats studied earlier (that is, those given 14% oxygen).

Peritonitis with pancreatitis occurred in 8% of rats in which large rectal temperature probes were used. Large rectal probes probably should be avoided in studies of long duration and in normoxic environments.

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Clinical Reports

Deep Neck Abscesses in Adults:
Management of a Difficult Airway

Donald J. Heindel, MD

Since the advent of effective antibiotics the incidence of deep neck abscesses has drastically decreased and mortality has gone from approximately 50% to less than 5%. However, the anesthesiologist will occasionally encounter this potentially life-threatening situation.

Case 1

A 21-yr-old woman was admitted with a 1-day history of fever, sore throat, and dysphagia. Medical history included two previous neck explorations for excision of a lymphangioma, but was otherwise noncontributory. Physical examination revealed moderate trismus and bulging of the right pharyngeal mucosa with erythema extending from the soft palate down to the piriform sinus. The epiglottis was displaced to the left. She was admitted for close observation and administration of intravenous penicillin and gentamycin. Six hours after admission the patient developed increasing respiratory distress. A computed axial tomography (CAT) scan of the neck revealed a large right neck phlegmon, a questionable abscess, and deviation of the airway to the left. After anesthesiologic consultation, the patient was scheduled for tracheostomy under local anesthesia to be followed by a right neck exploration under general anesthesia.

The tracheostomy was performed with minimal sedation while 100% oxygen was administered via a circle system. General inhalational anesthesia was then begun via a cuffed Schiley tracheostomy tube. An infected lymphangioma of the parapharyngeal space was incised and drained, after which the patient was transferred to the intensive care unit (ICU). She responded well to antibiotics and was transferred to the ward the next day. The tracheostomy was decannulated on the fifth postoperative day and the patient was discharged on the eighth postoperative day.

Case 2

A previously healthy 26-yr-old man was admitted with increasing pain and swelling after extraction of the right lower third molar. Despite intravenous antibiotics, swelling progressed until it extended from the right submandibular space inferiorly along the sternocleidomastoid muscle to the suprasternal notch. Airway compromise was confirmed by fiberoptic laryngoscopy and the airway was secured with a cuffed 6.0-mm nasotracheal tube passed through the left side of the nose using an awake, blind technique.

A right, deep neck abscess involving the right submandibular and pharyngomaxillary spaces was then diagnosed by direct examination and confirmed with soft tissue x-ray films of the neck. The patient was immediately scheduled for incision and drainage of the neck abscess, with possible tracheostomy. Prior to surgery, the 6.0 mm nasotracheal tube developed a cuff leak so occlusive pressure could not be maintained and the prevention of aspiration could not be assured. However, spontaneous ventilation remained adequate.

The patient was brought to the operating room where, after preoxygenation and the administration of 3 mg of curare, anesthesia was induced with 200 mg of thiopental, 200 mg of lidocaine, and 1% iso-

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flurane, followed by 100 mg of succinylcholine. The surgeon was immediately available to perform an emergency cricothyroidotomy if necessary. Under direct oral laryngoscopy, a 7.0 mm endotracheal tube was positioned in the oral cavity and the 6.0 mm nasotracheal tube, seen passing through the cords, was removed. Immediately upon extubation the abscess ruptured obliterating the posterior pharynx with purulent, bloody fluid. The surgeon immediately started to perform a cricothyroidotomy. No attempts at mask ventilation were made. The cricothyroidotomy was difficult because of extensive edema and required approximately 4 min. During this time the patient's heart rate dropped to 20 beats/min but immediately responded to IV atropine. When ventilation became possible, wheezing was noted. Suctioning of the trachea through the cricothyroidotomy produced copious, bloody, purulent fluid. It was estimated that the patient had aspirated more than 30 ml of purulent material. The neck was incised and drained as expeditiously as possible and the patient was transferred to the ICU.

Postoperatively the patient was alert, oriented, and neurologically intact. The subsequent aspiration pneumonitis was treated with antibiotics, mechanical ventilation, and positive end-expiratory pressure. The remainder of the hospital course was complicated by bilateral pneumothorax, as well as pneumomediastinum and pneumopericardium. Despite intensive care, the patient died on the 11th postoperative day, of complications secondary to aspiration pneumonitis.

Case 3

A 35-yr-old, obese woman presented with a 4-day history of facial and neck swelling after dental work on carious teeth. On admission the patient was febrile with swelling of the right submaxillary, submental, and pterygomandibular spaces with associated trismus. A nasopharyngeal fiberoptic examination confirmed the swelling but revealed no inflammation around the vocal cords or epiglottis. She was admitted for observation and treatment with intravenous antibiotics. Six hours later the patient began complaining of dysphagia as well as increasing swelling. A CAT scan of the neck revealed a probable abscess of the right masticator space. She was transferred to the operating room where successful, awake, nasal, fiberoptic intubation was performed by the anesthesiologist, with the surgeons prepared to perform an emergency tracheostomy. When the airway was secured, general anesthesia was induced and the surgeons explored the right neck. The patient's right masticator space abscess was incised and drained and the teeth previously operated upon were removed. Postoperatively, the patient was transferred to the ICU with the nasotracheal tube still in place. Her infection responded well to intravenous antibiotics and she was extubated on the second postoperative day. She was discharged from the hospital on the tenth postoperative day.

Discussion

Management of patients with a deep neck abscess consists of airway management and IV antibiotics, with incision and drainage of the abscess as necessary. Our anesthetic expertise is called upon for help in the management of the airway as well as for the administration of anesthesia for surgical incision and drainage. A working knowledge of the fascial planes of the neck is essential in these cases (1–4). In general, the hyoid bone is the most important structure in the neck which limits the spread of infection. Levitt (5) divides the fascial plains into 1) those involving the entire length of the neck (i.e., retropharyngeal, prevertebral, visceral vascular); 2) those above the hyoid bone (i.e., submandibular, pharyngomaxillary or parapharyngeal, masticator, parotid, and peritonsillar); and 3) those below the hyoid bone (i.e. anterior visceral). Although these spaces have discrete boundaries, it is not uncommon for an advanced infection to spread to adjacent spaces.

Before surgery, full assessment of the airway is necessary. Such assessment must include both direct and indirect examinations as well as needle aspiration of a potential abscess when indicated. Soft tissue x-ray films of the neck are necessary for evaluating retropharyngeal or epiglottic involvement and can demonstrate air or gas in the cervical tissues. Dental (panorex) x-ray films are used to locate odontogenic processes, which are responsible for the majority of deep neck abscesses. Computed axial tomography scans greatly help diagnose as well as accurately locate deep neck abscesses (6–8). In case 1, the CAT scan was particularly helpful because the lack of external cervical swelling was misleading. Only the CAT scan demonstrated the true extent to which the airway was compromised.

Although some abscesses, such as peritonsillar abscesses, can be drained under local anesthesia, most of these infections must be drained under general anesthesia. There is common agreement that the airway should be secured for general anesthesia, but there is controversy over the mode of intubation, particularly because each case is unique. After complete

airway assessment, the surgeon and anesthesiologist must jointly decide on the best method of securing the airway.

Because of the ever-present potential of rupturing the abscess, a tracheostomy should be considered first. However, there are real risks with tracheostomies performed in these cases. The most common early local complications are bleeding, dislodgement of the tracheostomy tube and obstruction of the cannula. Other complications include subcutaneous emphysema, stomal narrowing, wound infection, pneumothorax, and cord paralysis. Late complications, rarely seen under 1 week, are tracheal stenosis, tracheoesophageal fistula, major artery erosion and late infections. Another problem unique to deep neck abscesses is that the tracheostomy site may be involved in the infection, as in case 2. This infection is a relative contraindication to tracheostomy.

The greatest risk with oral or nasal intubation is rupture of the abscess with aspiration of purulent fluid, which can be devastating, as in case 2. With this in mind, awake intubation is preferable. Optimally, this procedure should be attempted only if the abscess is located in an area away from the route of intubation. In case 3, the abscess was located in the masticator space with swelling extending into the submandibular space. This area could be avoided using a fiberoptic laryngoscope for awake, nasal intubation. Tracheostomy was not performed, and the patient was successfully intubated nasally. In case 1 the abscess was located in the parapharyngeal space and deviated the airway to the left. Although fiberoptic laryngoscopy for intubation might have been successful, the risk of abscess rupture during this procedure was too great and a tracheostomy was performed. The risk was particularly great since the optics of the fiberoptic scope eliminate any depth perception and the magnification distorts the actual distance to objects.

Case 2 is an argument for early tracheostomy. The reported potential complications of tracheostomy were weighted heavily in the decision to attempt reintubation rather than do a tracheostomy. In retrospect, the patient should not have been extubated. Rather, a tracheostomy under local should have been performed, despite the presence of infection at the tracheostomy site. Perhaps a CAT scan would have revealed the true extent of the infection and an alternate course would have been used. Another possibility might have been placement of a pharyngeal pack to prevent the cuff leak while proceeding with surgical incision and drainage of the abscess. However, this procedure itself carries the inherant risk of rupturing the abscess.

In summary, deep neck abscesses can be life-threatening in otherwise healthy patients. Airway compromise should always be considered and the potential for abscess rupture is ever-present. A thorough evaluation of the airway is an absolute necessity, and should include use of the CAT scan. Securing the airway must be a joint venture involving surgeon and anesthesiologist. Tracheostomy should be considered early and be performed before intubation in questionable cases, even though tracheostomy has its own inherent risks in cases such as these. If nasal or oral tracheal intubation is undertaken, an asleep or blind intubation is more hazardous than an awake, fiberoptic intubation. During intubation, the surgeon must always be ready to perform an emergency cricothyroidotomy immediately.

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Pain from an Invasive Facial Tumor Relieved by Lumbar Epidural Morphine

Shaun P. Sullivan, MD, and David A. Cherry, MB, BS, FFARACS

The administration of epidural morphine and meperidine in the management of acute and chronic pain has been the subject of considerable clinical research after the identification of opiate receptors in laminae 1, 2, and 5 of Rexed in the dorsal horn of the spinal cord grey matter (1,2).

Patients with pain of malignant origin have been able to achieve satisfactory pain relief with a variety of implantable intraspinal systems for opioid administration (1). These systems are indicated when primary methods for eradication of tumor fail concurrent with the failure of systemically administered opioids to provide adequate pain relief without unacceptable side effects (1).

Because delayed respiratory depression may occur after lumbar epidural administration of opioids, the cephalad spread of epidural opioids has been studied using cervical cerebrospinal fluid (CSF) sampling (3). Passive cephalad diffusion of opioids such as morphine and meperidine from the lumbar CSF is hypothesized to occur and may take 60 min to reach significant concentrations at the cervical level. It is therefore thought that pain mediated by neurones entering the spinal cord from the thoracic, cervical, or even cranial nerves can be treated effectively using opiates injected into the convenient lumbar epidural route. We report a case of pain relief from an invasive parotid cancer by morphine administered through an indwelling lumbar epidural catheter.

Case Report

A 48-yr-old man presented originally in August 1983 with the sudden onset of left arm and leg weakness and dizziness. He had been experiencing left facial numbness for 1 month. Over the next 24 hr all symptoms resolved spontaneously except for a constant tingling sensation over the left side of his face. Medical history was noncontributory and examination showed no focal neurologic deficit. Blood pressure was normal. A CT scan of the head and a digital subtraction angiogram were within normal limits. Routine serum screening tests showed elevated levels of cholesterol and triglycerides.

The patient was diagnosed as suffering from right-sided transient ischemic attacks, and was discharged on an appropriate diet.

The patient had no further symptoms except for persistent left facial tingling until October 1984 when he presented with a left parotid mass. This was biopsied and found to be a squamous cell carcinoma. Resection was attempted but removal of the tumor was incomplete. In June 1985 the patient had a palliative revision of the parotid operative site with removal of his left ear and a full thickness muscle flap from his left trapezius. Palliative radiotherapy was administered. Neither the surgical palliation nor radiotherapy reduced tumor invasion and by March 1986 the patient was referred to the Flinders Pain Management Unit for pain therapy.

The patient complained of severe pain that was not relieved by oral opioids. The pain was primarily in his left eye and temple, and there was phantom pain in the left ear. The pain was recorded by the patient as between 5 and 8 cm on the 10-cm visual analogue scale. He also suffered from vertigo, nausea, vomiting and excessive drowsiness.

On examination the patient had a facial nerve palsy on the left. He had tumor invading the structures on the left side of his face below the eye and some sloughing of the muscle flap. A regimen of gradually increasing doses of carbamazepine, amitriptyline, paracetamol, and stemetil suppositories was initiated. This adjuvant therapy supplemented the oral morphine mixture and provided some additional pain relief. However, vertigo, nausea, and drowsiness continued to be clinical problems.

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In late March 1986, the patient returned with increasing pain. The side effects of the oral medication were becoming intolerable and pain relief was inadequate. A temporary lumbar epidural catheter was inserted to evaluate the effect of epidural morphine on the patient's facial pain. Morphine, 10 mg in 10 ml of normal saline, was injected via the catheter with excellent pain relief after 30 min. There was no immediate or delayed respiratory depression. Three hours after injection the pain began to return slightly and a single cervical CSF sample was taken from the C-7–T-1 interspace through a 25-gauge spinal needle. The morphine level in CSF was determined by high pressure liquid chromatography with electrochemical detection (4) to be 55 ng/ml. An indwelling epidural portal catheter was inserted the following day in the L2-3 interspace, as previously described by Cherry et al. (5). The patient lived for an additional 6 weeks and had adequate relief of facial pain from doses of epidural morphine between 10 and 20 mg every 3–4 hours. The vertigo and nausea continued to be relatively resistant to drug therapy, but the patient described himself as being relatively free from pain and much less sedated.

Discussion

Chronic indwelling epidural catheters for morphine administration in the relief of cancer pain have been utilized in patients with pelvic, abdominal, and thoracic tumors, but their use for pain relief from head and neck cancers has not been reported. The lumbar epidural approach is most convenient and probably carries a smaller risk of morbidity.

Rostral migration of morphine from the lumbar epidural space to cervical and intraventricular CSF has been suggested by clinical observations (6), and more recently, by CSF sampling at the C-7–T-1 interspace in cancer patients with indwelling lumbar epidural catheters (3). In our patient, there was a significant level of morphine in the cervical CSF and relief of pain from the invasive parotid tumor, presumably innervated by the spinal tract of the trigeminal nucleus, the glossopharyngeal nerve, and the upper cervical nerve roots, was achieved.

Morphine administered by the lumbar epidural route can have significant analgesic activity in both CSF and plasma. Vascular uptake of morphine from the epidural space might contribute to pain relief after lumbar epidural administration (7).

After the lumbar epidural administration in cancer patients of 10 mg of morphine in 10 ml of normal saline, there is rapid vascular uptake (3). The time taken for this dose to reach peak blood concentrations varies between 2 and 10 min, and the mean peak blood concentration is 110 ± 32 ng/ml (range, 76–182). This blood concentration declines rapidly and is below the minimum effective concentration (MEC) for morphine by 120 min. Pain relief persisting after this time must be explained by other mechanisms, such as the diffusion of morphine within the CSF to opioid receptors in the dorsal horn of the spinal cord, in the present case the spinal tract of the trigeminal nucleus. Our patient experienced pain relief for 3 hr, at which time pain began to return and the morphine concentration in the cervical CSF was 55 ng/ml. This indicates that a significant concentration of morphine was present in cervical CSF 3 hr after lumbar epidural administration. The minimal effective concentration of CSF morphine for the relief of chronic pain has not been accurately determined but is predicted to be in the range of 50–100 ng/ml (unpublished observations, D. Cherry).

Morphine appears in lumbar CSF within 15 min or less after lumbar epidural administration (8) and is in higher concentrations than in the plasma in many patients by that time. Lumbar CSF concentrations of morphine remain 100–200 times higher than those in plasma for several hours thereafter (9). After this appearance of morphine in lumbar CSF, there is a delay in the achievement of peak concentrations in cervical CSF (3). This peak occurs at 180 min and ranges from 500–747 ng/ml (3). Metrizamide and radionuclides also reach the fourth and lateral ventricles about 3–6 hr after lumbar intrathecal administration (10,11). This is despite an apparent absence of an active CSF circulation in the spinal subarachnoid space (12). Gustafsson et al. have shown that morphine distributes cephalad to the trigeminal nerve in rats after pharmacologic doses of lumbar intrathecal morphine (13). Morphine, a hydrophilic opioid, may act similarly to water soluble contrast media and passively diffuse cephalad in the CSF after lumbar epidural administration, penetrating to the spinal tract of the trigeminal nucleus lying close to the surface of the upper cervical cord.

Our patient suffered persistent vertigo, nausea, mild sedation and some vomiting while receiving epidural morphine. These side effects could be related to the invasive nature of the tumor, the known central side effects of lumbar epidural morphine, or, more likely, a combination of both mechanisms.

In conclusion, a patient presented with severe, intractable facial pain from an invasive parotid tumor. The patient was relieved of pain by injections of lumbar epidural morphine, which was found to be associated with significant levels of morphine in the cervical CSF.

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Cervical Epidural Implantable Narcotic Delivery Systems in the Management of Upper Body Cancer Pain

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The use of epidural narcotics represents a substantial advance in the management of cancer pain. In patients with a relatively short life expectancy, delivery of epidural narcotics may be carried out as needed, using either single injections or percutaneous catheters (1). For patients with longer life expectancies, a variety of totally implantable narcotic delivery systems (INDS) have been developed (2–7).

Previous reports on the use of INDS placed in the lumbar region demonstrated their efficacy in the management of pain arising in the lower trunk and lower extremities, but note that their efficacy is not as great in control of upper body pain (2). Neurolytic and neurosurgical procedures, therefore, are often advocated for palliation of intractable pain in the distribution of the cervical nerve roots (8). Seurini and Orsili, however, reported the use of cervical epidural morphine to treat neck pain in two cancer patients with good results and minimal side effects (9). We report our experience in 12 patients with upper body pain, 11 of whom experienced excellent relief with narcotics delivered into the cervical epidural space via an INDS.

Clinical Experience

Twelve patients (Table 1) were evaluated for intractable neck, shoulder, upper extremity, or upper thoracic pain of malignant origin by the Kansas City Pain Consortium. In all cases, the pain was unresponsive to oral narcotics, adjunctive drugs, radiation, and chemotherapy. The first eight patients were given a trial of lumbar epidural injections of morphine (up to 10 mg) without adequate pain relief. Trial administration of cervical epidural morphine was then carried out in all 12 patients, utilizing a single-injection technique in which an 18-gauge Hustead needle was introduced in the midline at the C6–C7 interspace. The epidural space was identified by the saline loss-of-resistance technique. After a negative aspiration test, 1 mg morphine dissolved in 6 ml preservative-free saline was injected through the Hustead needle. Eleven patients had excellent relief of pain within 1 hr and remained comfortable for an additional 10–24 hrs. No respiratory side effects were noted. One patient complained of transient pruritus. One patient was unable to assess the degree of pain relief after the trial dose of cervical epidural morphine because of mental confusion. This patient was excluded as a candidate for INDS implantation (10). The remaining 11 patients underwent placement of cervical epidural INDS.

All catheters were placed epidurally under direct visualization by hemilaminectomy under general anesthesia. The proximal tip of the catheter was placed between C-3 and C-5. The distal portion of the catheter was tunneled subcutaneously and attached to subcutaneous Radovan reservoir (Heyer Schulte, Chicago, IL). In eight patients, the reservoir dome was placed posteriorly in the upper back musculature, and in three patients it was placed on the anterolateral chest wall. Injections into all reservoirs were made within 48 hr of surgery. All INDS functioned without difficulty. There were no problems with respiratory depression.

The patients' families were instructed in the care and use of the INDS and usually could be trained to inject the INDS within 2–3 days. The patient was supplied with prefilled morphine sulfate syringes and all supplies necessary to prepare the INDS for injection.

Families and patients were instructed to inject morphine into the INDS at a time interval and dosage based on response to the initial trial doses. Most patients were initially managed with a single daily injection of 1–2 mg morphine dissolved in 6 ml saline. Tolerance gradually developed in all patients over the 6–8 weeks after implantation. This was initially treated by increasing the dose and frequency of injection of

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Table 1. Cervical INDS Patients

Patient number	Age/sex	Cancer type	Type of pain	Follow-up
1	53/M	Lung	Brachial plexopathy	Died 6 months 2 mg MS daily—good relief
2	68/M	Prostate	Bone pain and cervical radiculopathy	Died 4–5 months 1.5 mg MS daily—good relief
3	61/F	Breast	Chest wall pain	At 13 months 2 mg MS B.I.D., local steroid 3×—good relief
4	49/M	Thyroid	Brachial plexopathy	Died 3 months 2.5 mg MS B.I.D.—good relief
5	56/M	Lung	Brachial plexopathy Chest wall	Not implanted
6	63/M	Renal	Cervical radiculopathy	At 6 months 1.5 mg MS B.I.D.—good relief
7	49/F	Breast	Cervical radiculopathy Chest wall	At 8 months 2 mg MS B.I.D., local steroid × 2—good relief
8	68/M	Prostate	Cervical radiculopathy Bone pain	Died 7.5 months 2.5 mg MS B.I.D., local steroid × 1—good relief
9	64/F	Breast	Chest wall Cervical radiculopathy	At 6.5 months 2.0 mg MS B.I.D.—good relief
10	61/M	Lung	Chest wall Brachial plexopathy	At 17 months 2.0 mg MS B.I.D., local steroid × 4—good relief
11	47/F	Breast	Cervical radiculopathy	Died 4.5 months, 1.5 mg MS daily—good relief
12	67/F	Lung	Brachial plexopathy	Died 4 months 1.5 mg MS B.I.D.—good relief

the INDS. In no instance did an increase in dose, frequency, or both result in additional side effects. If tolerance continued to be a problem, the INDS was injected with local anesthetic and methylprednisolone (11).

Discussion

Narcotics injected into the lumbar epidural or subarachnoid space relieve lower body cancer pain (2–7). In spite of known rostral spread of morphine within the CSF (12), morphine injected in the lumbar area does not control upper body cancer pain in many patients. Cobb et al. (2) postulate that narcotics injected in the lumbar area do not provide high enough concentrations of narcotic to the upper thoracic or cervical cord to control pain mediated at these levels. Gourlay et al. (13) reported cephalad migration of "lumbar" epidural morphine into the cervical subarachnoid space, but the peak cerebrospinal fluid (CSF) concentration (approximately 360 ng/ml) after 10 mg morphine is significantly lower than the peak concentrations sampled in the lumbar region. Jourgensen et al. (14) noted lumbar CSF concentrations of 3200–3900 ng/ml after 8 mg lumbar epidural morphine, and Nordberg et al. (15) noted lumbar CSF concentrations over 1000 ng/ml after 6 mg lumbar epidural morphine. It is important to note that in the study by Gourlay et al. the morphine was not actually delivered into the lumbar epidural space. The delivery system described (16) utilized instead an epidural catheter, the tip of which rested in the midthoracic (T7–T8) region. We suspect that the peak cervical CSF morphine levels would have been even lower if the morphine had in fact been injected into the lumbar or low thoracic epidural space.

We placed morphine directly into the cervical epidural space in an attempt to achieve higher cervical CSF morphine concentrations and relieve upper body cancer pain. Treatment was initiated with a relatively low dose of morphine to avoid respiratory depression when injecting so close to the brain stem. No respiratory side effects were noted after the initial low dose or after the dose and/or frequency of injection was increased to treat tolerance.

The pharmacokinetics of morphine administered into the cervical epidural space have not been described. However, we believe on an anatomical basis that cervical epidural morphine will be present in the adjacent cervical CSF in greater concentrations than will be present with an identical dose injected in the lumbar region. The lumbar epidural space is approximately twice as large as the cervical epidural space (17). A given volume of solution injected into the cervical epidural space will cover more spinal segments than when the identical volume is injected into the lumbar epidural space. Therefore, injection of a given volume into the cervical epidural space will be exposed to more dural surface area for absorption into the subarachnoid space. The lumbar epidural venous plexus would also be expected to be more engorged in the sitting or upright position than the cervical epidural plexus, thus causing more systemic absorption of epidurally administered morphine in the lum-

bar region when compared with the cervical region. The presence of tumor within the epidural space may block the rostral spread of morphine (18). Even if complete blockage does not occur, an epidural mass would be expected to increase dependent venous engorgement, resulting in increased systemic absorption and decreased CSF morphine concentration. Injection into the cervical epidural space may bypass both of the problems. Because of the frequent inability of lumbar epidural morphine to control upper body pain of malignant origin, we have discontinued its use in this setting.

Injection of 1–2 mg morphine into the cervical epidural space provided excellent pain relief in 11 patients with upper body cancer pain. Cervical INDS were implanted for long-term administration of epidural narcotics. As tolerance developed, INDS were injected twice daily. No additional side effects were seen with this increase in frequency of injection. Five patients are currently alive and continue to experience good pain relief. One of these patients has used his INDS continuously for over 17 months without problems. No patient who received an INDS required a neurolytic block or neurosurgical procedure for pain control.

It appears that cervical administration of morphine via an INDS is a safe and effective approach to the palliation of upper body cancer pain.

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Anesthetic Challenges in Separation of Craniopagus Twins

Linda S. Georges, MD, Kelly W. Smith, MD, and K. C. Wong, MD, PhD

The incidence of craniopagus conjoined twins is estimated at one in 2.5 million births (1). It is the least common type of conjoined twinning, accounting for only 2% of the total (2). Although published reports of the anesthetic management of the separation of craniopagus twins have increased in the past 15 yr, the total number is quite small. In a 1967 review, Keats et al. (2) reported the separation of five sets of craniopagus twins. By 1977 two more sets of craniopagus twins were separated as reported by Jarem et al. (3). Since that time the only report of the separation of craniopagus twins published in the anesthesia literature came from this department in 1980 (4).

The separation of the twins at 18 months of age that we previously reported (4) was our first experience with the separation of craniopagus twins. These children are now living at home. One has a mild neurologic deficit, and the other has a more severe handicap. The current case has several important aspects of anesthetic management that differ from the first and deserve reporting. These include facial presentation, pharmacologic responses, and blood volume of the twins that is lower than predicted.

Case Report

The twins, X and Y, were diagnosed as craniopagus by prenatal x-ray and delivered by cesarian section at 36 weeks' gestation on March 9, 1984. They were normal in every way with the exception of their shared cranial vault. The attachment was craniopagus parietalis facing in opposite directions (Fig. 1). Because of their position they were nursed in the lateral position. The twins were transferred to the University of Utah Medical Center at 6 weeks of age for evaluation and staged separation. At the time, their combined weight was 7.6 kg.

Our first anesthetic experience with these twins was general anesthesia for cerebral angiography. Our primary concern was securing and maintaining the airway of each infant during the angiographic manipulations. Our prior experience alerted us to the possibility that the anesthetic requirements of one infant might vary greatly from the other (4). Therefore, two anesthesia machines, two monitoring systems, including end-tidal CO_2 and transcutaneous O_2, and two anesthesiology teams were used.

The infants were anesthetized with halothane by mask and intubated with 3.0-mm inner diameter (id) RAE preformed endotracheal tubes without a muscle relaxant. One was supported in the prone position; breathing spontaneously, while her sister was being intubated. Once the tube was taped securely in place, they were rotated and the second twin was intubated. Both infants were intubated without difficulty, but because they had been positioned on their chest or back, always facing left; we were not able to rotate their necks to face completely anteriorly. For this reason, physical therapy was begun before the first anesthetic experience to improve neck mobility of both twins.

During this initial 4-hr procedure, the anesthetic requirements of both twins were quite similar, even though their vital signs were at times very different. Y's rectal temperature was as much as 2°C lower than X's and her heart rate was 5–15 beats/min slower, but X's blood pressure was approximately 10 mm Hg lower than Y's. Toward the end of the procedure, because we had seen very little anesthetic interaction between them, we gave X IV atropine (total dose 0.1 mg) and ephedrine (total dose 5 mg) in incremental doses to see what cardiovascular effects they might have on Y, to improve our understanding and management of the patients in the future. Despite a peak increase in heart rate of 25 beats/min and a 14-mm Hg increase in blood pressure in X, no change in vital signs was apparent in Y. Both infants were awake and extubated in the angiography suite within 20 min of completion of the procedure. Angiography indicated that the children shared a common superior sagittal sinus and had a major arterial connection between their right cerebral arteries.

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Figure 1. Conjoined twins at 6 weeks old and 7.6 kg combined weight. Parental permission for publication.

During the following 4 months, the twins underwent four staged craniotomies, repeat cerebral angiograms, and the placement of tissue expanders under the scalp in preparation for the final separation procedure. Following are some of the pertinent experiences from those procedures.

After the first two procedures, we began alternating the twin in which anesthesia would be induced first in order to evaluate the anesthetic crossover effect from one to the other. During induction one infant would be supported prone and allowed to suck on a pacifier while anesthesia was induced in the other by mask in the supine position. During the induction and intubation of the first twin, the other was observed for any sedative effects coming through their shared circulation. There was never any apparent sedation of the second twin despite a higher blood pressure sometimes present in the infant in whom anesthesia was being induced first.

The twins responded hemodynamically as if they had basically separate circulations. This was supported by their consistently different hematocrits before and after procedures common to both infants. It is also of interest that their blood volumes were closer to 65 ml/kg rather than the estimated 80 ml/kg at 7 weeks of age. This was evident by an increase in their hematocrits from 31 and 34% to 37.5 and 40%, respectively, by the administration of 125 ml packed red blood cells (hematocrit 60%) administered to each (total weight 9 kg). The twins appeared to be equal in size.

The Final Separation

The final separation of X and Y was started on the morning of September 13, 1984. The twins were 6 months old with a combined weight of 13 kg. They were medicated with phenobarbital to prevent seizures. Each twin was premedicated with atropine, 0.1 mg IM, and they were brought to the operating room awake and alert. Precordial stethoscopes, automatic blood pressure cuffs (Omega Neonatal/Pediatric), pulse oximeters (Nellcor), and electrocardiogram leads were placed on the patients. Anesthesia was induced first in one and then in the other with halothane, nitrous oxide, and oxygen by mask. They were intubated with 3.5-mm id uncuffed oral endotracheal tubes, and, after correct positioning of the tubes was assured, the tubes were secured with benzoin and adhesive tape. Esophageal stethoscopes were inserted, and the eyes heavily lubricated and taped shut. Urinary catheters and rectal temperature probes were also inserted. A 22-gauge intravenous catheter was inserted in each infant. Radial arterial and forearm venous catheters were placed with surgical cutdowns in the supine position. Femoral catheters were avoided because of poor pulses secondary to multiple arteriograms.

Anesthesia was maintained with halothane, oxy-

Table 1. Clinical Summary

Parameter	Twin X	Twin Y
Estimated blood loss (ml)	2600	1400
Intraoperative fluids (ml)		
Whole blood	2250	1365
Packed red blood cells	250	0
Crystalloid	1010	800
Fresh frozen plasma	250	350
Platelets	200	50
Calcium gluconate (mg)	2010	1800
$NaHCO_3$ (mEq)	15	25
Preoperative Hct (%)—9/12/84	42	39.5
Last Hct in operating room—9/14/84	34.3	34.5
Postoperative 2 hr Hct—9/14/84	27.4	25.0
Postoperative day 1 Hct—9/15/84	31.7	24.1
Postoperative day 2 Hct—9/16/84	26.4	32.7

gen, and nitrous oxide. Fentanyl and pancuronium were added as needed. One anesthesia machine was equipped with a pediatric circle system and the other with a CPRAM partial rebreathing system. Different systems were used because of the preferences of the anesthetic teams. Ventilation was controlled in both infants using Ohmeda 7000 pediatric ventilators, with Pa_{CO_2} levels maintained between 28 and 35 mm Hg. After insertion of intravascular catheters, the twins were placed in the left lateral decubitus position on gel pads. All pressure points were padded with foam rubber to avoid any damage as a result of remaining in the same position for a prolonged period. Warming blankets were placed under and on top of the infants, and all intravenous and irrigation fluids were warmed.

Arterial blood gas tensions, electrolyte levels, serum glucose, complete blood counts, and coagulation profiles were measured as indicated during the procedure. Early in the operation, both infants had moderate negative base deficits (5–10 mEq/L), which were corrected with sodium bicarbonate. The problem did not recur. Temperatures remained stable throughout the procedure. The patients' phenobarbital schedule was maintained during the anesthetic.

From the beginning of the procedure and during the course of the surgery, X had a lower blood pressure (70/50–60/45 mm Hg) and required less anesthetic than Y (90/60–76/50 mm Hg). Blood loss was very difficult to estimate, and we depended on serial hemoglobin and hematocrit measurements and the responses of each infant to anesthesia and to transfusion in deciding how much blood to administer. As the case progressed, X was given a larger volume of transfused blood than Y to maintain an acceptable blood pressure and hematocrit. When visually comparing the apparent blood loss in the surgical field, there did not seem to be a difference between the two twins despite an arterial pressure 20–40 mm Hg higher in Y. At times X required large volumes of blood and very low anesthetic concentrations, whereas Y required increasing anesthetic depth with fewer transfusions. It appeared that the most blood loss for several hours was from X. Overall X was given 2250 ml whole blood, 250 ml packed red blood cells, 250 ml fresh frozen plasma, 200 ml platelets, and 1010 ml crystalloid. In contrast, Y was given only 1365 ml of whole blood, 350 ml fresh frozen plasma, 50 ml platelets, and 800 ml crystalloid. Both infants required large amounts of calcium gluconate to maintain normal ionized calcium levels. The clinical summary is presented in Table 1.

The twins were completely separated at 08:55 on September 14, 1984. The two operating tables, which had been positioned end to end, were moved apart while sterile fields were maintained. The neurosurgeons and two plastic surgery teams then completed the procedure by covering the brains with lyophylized dura, scalp flaps, and cadaver skin graft.

At the end of the procedure, each infant was extubated and reintubated nasally with a 3.5-mm id uncuffed endotracheal tube to simplify postoperative ventilatory care. They were transported to an intensive care unit (ICU) after over 31 hr of anesthesia and 27.5 hr of surgery. Within 30 min of arrival in the ICU, they were opening their eyes and beginning to respond to stimulation with purposeful movements. They were mechanically ventilated, mildly sedated, and weaned from respiratory support over the next 3 days. Initially both infants had a mild metabolic alkalosis (pH 7.49–7.55). This resolved over the following 24 hr, and each subsequently maintained a normal pH. F_{IO_2} was gradually decreased from an initial level of 0.5 to 0.3, and the intermittent mandatory ventilation decreased from an initial setting of 30 breaths/min to 4 breaths/min by the end of the second postoperative day. Both infants were extubated on postoperative day 3 and begun on oral feedings on day 5.

One year after their separation, the twins are active and growing (Fig. 2). Each has a residual left hemiparesis and has had episodes of meningitis. In addition, each child has returned to the operating room for shunt placement and revision, Tenkoff catheter insertion, and revisions of scalp and dural flaps.

Comments

We found this set of craniopagus twins to be unusual for several reasons. First, at the age of 7 weeks and a combined weight of 9 kg, their blood volume ap-

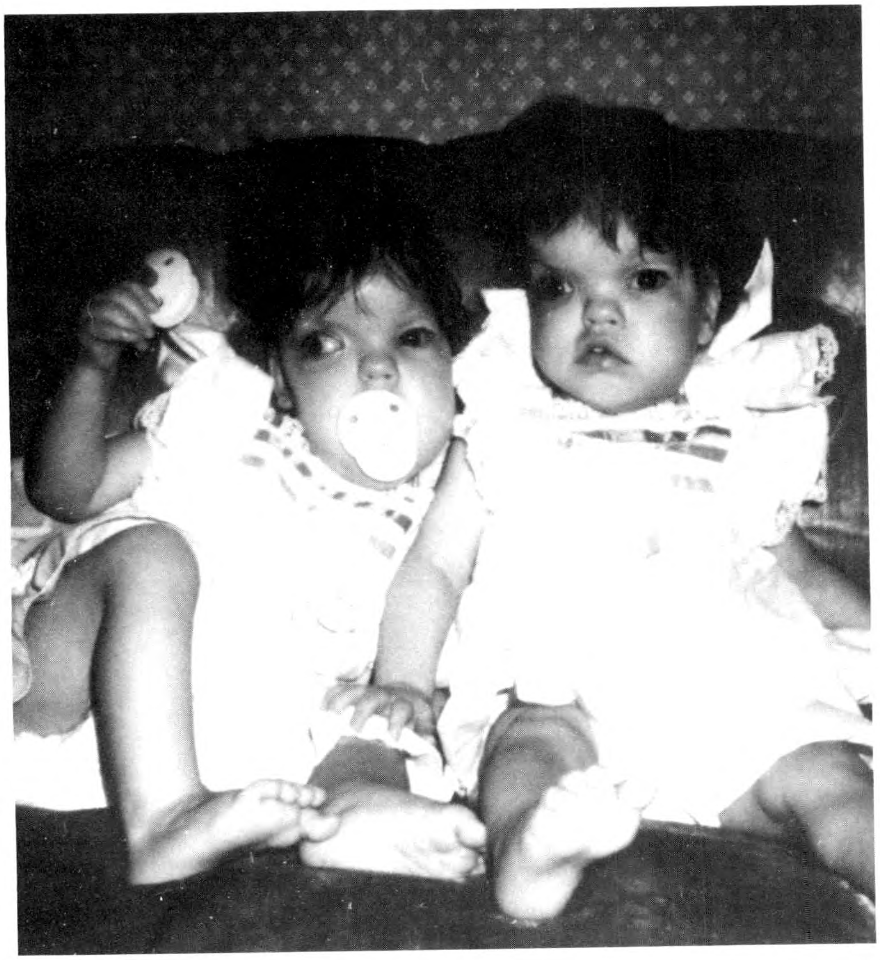

Figure 2. At 1 yr postoperative, 18 months old and approximately 10 kg each. Parental permission for publication.

peared to be closer to 65 ml/kg than the 80 ml/kg we had estimated.

Second, despite a shared superior sagittal sinus and a right middle cerebral artery anastamosis, these twins had predominantly separate circulations. Their responses to anesthetic agents, both inhaled and intravenous, as well as to inotropes, supported this conclusion. In addition, their hematocrits remained consistently unequal while they were still conjoined. A possible explanation for this unexpected finding is that the twins essentially had separate functional venous circulation of the head. The cerebral angiograms showed separate torcular Herophili, which is the dilated junction of three tributary sinuses: the superior sagittal, the straight, and the occipital with the two large transverse sinuses. Venous drainage of the brain is largely dependent upon the functional intergrity of these venous sinuses. Unlike our previous experience with conjoined twins (4), these twins did not respond to pharmacologic interventions in the same manner from one anesthetic experience to the next. In other words, they had to be treated as separate patients as well as different patients each time they were anesthetized. We can offer no good explanation for these observations.

Third, airway management in these infants required considerable vigilance. The obvious problems associated with the infants facing in opposite directions were compounded by their limited neck mobility. Physical therapy had made great improvements in this condition by the time of the final separation. Of utmost importance during each induction was the maintenance of spontaneous ventilation in the prone twin while anesthesia was induced and tracheal intubation performed in her supine sister. This allowed for separate control of each airway.

Estimation of total and individual blood losses was quite difficult because of the use of generous amounts of irrigation and the volume of blood on the drapes. The infants' hematocrits were used to indicate when whole blood was necessary, the objective being maintenance of each twin's hematocrit around 40%. Because of the large volume of blood replacement, coagulation profiles were serially measured and the

infants treated with fresh frozen plasma and platelets as needed to maintain normal values.

Ionized serum calcium was also repeatedly measured. Both infants required approximately 2 g of calcium gluconate in 100–200-mg increments during the procedure to maintain ionized calcium levels in the normal range. Calcium gluconate was used in preference to $CaCl_2$, because the latter can potentiate metabolic acidosis from the chloride ions, and calcium gluconate is less irritating to small peripheral veins. The important role of calcium in maintaining myocardial contractility was clearly demonstrated as blood pressure, pulse pressure, and auscultated heart tones improved with each dose. Ionized calcium is also important for normal coagulation. By maintaining normal ionized calcium levels, as well as by the administration of platelets and fresh frozen plasma, neither twin developed a bleeding diathesis in spite of the large quantity of blood transfused.

Maintenance of normal body temperatures in these infants during prolonged surgery was a serious problem. Our care included the use of warming blankets, warmed intravenous fluids and blood products, warming lights, and plastic body wraps, and control of the ambient temperature in the operating room. X's rectal temperature ranged from 36.0 to 37.2°C during the final procedure; Y's was more variable at 34.4 to 38°C. Both twins were normothermic upon arrival in the ICU.

Finally, adequate personnel and planning on the part of the anesthesiology team cannot be stressed enough. Our assignment of a resident and staff anesthesiologist to each infant allowed for coordination of complex intraoperative tasks and for the much-needed rest periods that assured continued vigilance during the prolonged procedure. Teamwork was essential to our management of these twins throughout the series of their separation procedures.

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Onset of Neuromuscular Blockade with Pancuronium in Children with Congenital Heart Disease

V. Maxim Lucero, MD, Jerrold Lerman, MD, FRCPC, and Frederick A. Burrows, MD, FRCPC

It has been suggested that intravenous anesthetic agents have a more rapid onset of action in children with congenital heart disease (CHD) who have right-to-left (R → L) shunting of blood and a slower onset in those who have left-to-right (L → R) shunting of blood than in children without CHD (1,2). Maunuksela and Gahiker investigated the use of pancuronium in children with CHD (3). They found no difference in either the dose requirement of pancuronium or the time to the onset of neuromuscular blockade between children with R → L and L → R CHD. However, they assessed the neuromuscular blockade subjectively, by palpating the twitch of the abducted thumb. To assess neuromuscular blockade in a more quantitative fashion, we compared both the time to 95% twitch depression and the intubating conditions in children with R → L shunts with those with L → R shunts who were paralyzed with pancuronium. We then compared these two groups with a group of children without CHD described previously (4).

Methods

With approval from our Human Research Committee, 30 children with CHD (R → L or L → R shunts), ages 2–8 yr were studied. All children with R → L shunting had Tetralogy of Fallot (n = 11) and were clinically cyanotic (oxygen saturation ≦ 90% breathing room air). Those with L → R shunting had ASD primum septal defect (n = 1), ASD secundum septal defect (n = 11), atrioventricular septal defect (n = 1), ventricular septal defect (n = 5), or patent ductus arteriosus (n = 1). The children were all ASA III, fasting, and premedicated with oral or rectal pentobarbital 2 mg/kg, and intramuscular morphine sulfate 0.2 mg/kg and atropine 0.02 mg/kg. Children were excluded from this study if there was evidence of neuromuscular or renal disease, if serum electrolytes were abnormal, or if a difficult intubation was anticipated. Preinduction monitoring included an ECG, precordial stethoscope, blood pressure cuff, Doppler arterial probe, and pulse oximeter. An intravenous (#20 angiocath) was then inserted in a dorsal vein of the hand or a saphenous vein in the foot. After preoxygenation anesthesia was induced with intravenous ketamine 1–3 mg/kg. Anesthesia was maintained with supplemental doses of ketamine as necessary and oxygen by face mask. Ventilation was spontaneous. Rectal temperature was monitored after induction of anesthesia.

The ulnar nerve was stimulated at the wrist using supramaximal square waves of 0.2-msec duration at a frequency of 0.15 Hz. The stimuli were delivered by a Grass S4 nerve stimulator through an SIU5 isolation unit. The force of thumb adduction was measured using a Grass FT03 force transducer and recorded on a Gould no. 2200S recorder. After a stable twitch response was obtained (control), each child was paralyzed with a rapid intravenous injection of pancuronium 0.15 mg/kg. When the twitch was depressed 95% below control, the trachea was intubated. The intubating conditions were assessed by the attending staff according to the criteria of Lund and Stovner (5).

These children were compared with a group of children without CHD (control) who were anesthetized with intravenous thiopentone (5 mg/kg) and atropine (0.02 mg/kg) and then paralyzed with pancuronium (0.15 mg/kg) as described previously (4).

Statistical significance ($P < 0.05$) was determined using analysis of variance, the Student-Newman-Keuls test, and the Fisher exact test.

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Table 1. Patient Characteristics

	Age (yr)	Weight (kg)	Hemoglobin (g/L)	Time to 95% twitch depression (secs)	Heart rate (beats/min)
Group 1 (R → L shunt)	3.7 ± 1.3	14.2 ± 1.7	168.7 ± 22.2	137.9 ± 51.0[b]	129.9 ± 40.0
Group 2 (L → R shunt)	4.7 ± 1.5	16.7 ± 4.1	124.9 ± 10.1[a]	118.7 ± 31.3[b]	152.1 ± 17.1
Group 3 (Control)	4.1 ± 1.9	17.9 ± 4.1	133.2 ± 4.2[a]	80.3 ± 21.8	132.9 ± 10.1

Data are means ± SD.
[a]$P < 0.05$ compared with group 1.
[b]$P < 0.05$ compared with group 3.

Results

There were no significant differences in age and weight among the three groups of children (Table 1). Hemoglobin was significantly greater in the group with R → L shunting as compared with the group with L → R shunting ($P < 0.05$). The time to 95% twitch depression did not differ significantly between these two groups with CHD. However, the times to 95% twitch depression for both CHD groups were significantly prolonged compared with the group of children without CHD (4). There was no significant difference in rectal temperatures between the two CHD groups. The mean heart rates (± SD) immediately before the intravenous injection of pancuronium 0.15 mg/kg did not differ significantly between the two groups with CHD or between those with CHD and the group without CHD. The intubating conditions were excellent in all patients studied.

Discussion

The results of the present study are consistent with previous studies (3), but are contrary to the classical teaching that the speed of onset of intravenous drugs is more rapid in patients with R → L shunts and slower in patients with L → R shunts than in patients without intracardiac shunts (1,2). This inconsistency may be attributed to several factors that require consideration.

The delayed onset of action of pancuronium in children with L → R shunting may be attributed to the recirculation of pancuronium through the pulmonary circulation and the resultant delay in reaching the neuromuscular junction (1,2).

The delayed onset of neuromuscular blockade in children with R → L shunts in this study may be attributed in part to an increased volume of distribution, a decrease in cardiac output and muscle blood flow, and an increased protein binding in this group of children compared with children without CHD. The volume of distribution of pancuronium is limited to the extracellular fluid compartment (6,7). In children with R → L shunts, the volume of the extracellular fluid compartment is increased secondary to an increase in the total blood volume resulting from polycythemia (secondary to the hypoxia of R → L shunting). Cardiac output and muscle blood flow may be reduced in these patients. The circulation time in children with R → L shunts is increased up to twofold (7,8). This, together with the increased viscosity, reduces the velocity of blood flow in the capillary and venous systems and may decrease the venous return to the heart. However, the increased blood volume in patients with polycythemia will also increase venous return. The net effect of all of these factors on cardiac output is likely to be small (8). Thus in a patient with R → L shunting, the speed of onset of neuromuscular blockade with pancuronium may be slowed because there is a relative increase in the volume of distribution of the drug, an increased circulation time, and a decreased blood flow through the microcirculation.

In infants and young children, cardiac output is heart rate dependent since the stroke volume is fixed (9). Although cardiac output was not measured in this study, the heart rate immediately prior to administration of pancuronium did not differ between either group with CHD and the control group studied previously. This suggests that the cardiac output did not differ among all three groups. It is unclear whether stroke volume, myocardial contractility, or the distribution of cardiac output was significantly different in the children with CHD compared with those without CHD. If cardiac output were reduced, then these factors could account for the slower onset of neuromuscular blockade with pancuronium in children with CHD. Further studies of the pharmacokinetics of drugs and the distribution of cardiac output in children with CHD are required in order fully to explain these results.

We conclude that the time to 95% twitch depres-

sion with pancuronium 0.15 mg/kg in children with R → L intracardiac shunting is not significantly different from that in children with L → R shunting but is 50–75% longer than in children without cardiovascular anomaly. Pancuronium 0.15 mg/kg may not provide optimal intubating conditions for a rapid sequence induction or rapid tracheal intubation in children with CHD.

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Postdural Puncture Headache after Continuous Spinal Anesthesia

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The technique of continuous spinal (subarachnoid) anesthesia (CSA) for administration of intermittent doses of local anesthetic is well established (1–7). It was first mentioned in 1907 by Dean (1), a British surgeon, who wrote of placing a needle in the subarachnoid space and leaving it in situ to facilitate reinjection. In 1944 Tuohy (2) reported placement of a ureteral catheter in the subarachnoid space using a Huber point needle.

This technique has two main advantages. The first is that the duration of anesthesia can be tailored to lengthy surgical procedures without the risk of the local anesthetic wearing off, as might be the case with single-injection spinal anesthesia. The other advantage is that small doses of local anesthetic can be administered intermittently until an adequate level of anesthesia is obtained, thus minimizing the risk of cardiovascular or respiratory disturbances, which is important, particularly in elderly or high-risk patients.

In recent years, continuous spinal anesthesia has fallen into disuse as reflected by the paucity of references to it in the recent literature (6) and in the current textbooks (3–5). Some of the reasons voiced for this disuse is fear that the large-bore needle used, 16–18-gauge, would result in an unacceptably high incidence of postdural puncture headache (PDPH) (5,8), and that there may be some risk of neurological sequelae or infection associated with a catheter in the subarachnoid space (9).

Since its introduction in this hospital 3 yr ago, continuous spinal anesthesia has been routinely used for patients in whom spinal anesthesia is indicated when the duration of surgery is anticipated to exceed 2–3 hr.

There is a slight risk of PDPH after single-injection spinal anesthesia. The incidence decreases, however, with increasing age of the patient and with decreasing needle size. The overall frequency varies from 0.24 to 37% (10–15). However, little is known about the incidence of PDPH after CSA. No prospective studies have been performed, but the few retrospective ones that have been published suggest that the incidence is low (6,7).

The purpose of this prospective study was to investigate the incidence of PDPH in patients after CSA.

Patients and Methods

One hundred and seventeen patients who underwent surgery of the leg or lower abdomen in whom continuous spinal anesthesia was indicated were studied. The type of surgery performed is shown in Table 1. Informed consent was obtained, and approval from the local ethical committee was granted.

In addition to the usual contraindications to spinal anesthesia, patients with a history of migraine or senile dementia were excluded from the study. The study data were stored and analyzed on an IBM PC computer using the SYSTAT Data Program.

Anesthetic Technique

The patients were premedicated as deemed appropriate by the anesthesiologist supervising the case. Lumbar puncture was performed with the patient either sitting or in the lateral decubitus position, after an intravenous infusion of 200–500 ml of crystalloid solution. Through a suitable interspace (L2–3, L3–4, or L4–5) under aseptic conditions, the subarachnoid space was entered using an 18-gauge Hustead needle, with the needle bevel parallel to the direction of the dural fibers. A 20-gauge, 90-cm nylon epidural (Encapsu-

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Table 1. Type of Surgery

Procedure	Number and percent of patients
Peripheral vascular surgery	35 (30%)
Orthopedic surgery	36 (31%)
Genitourinary surgery	31 (26%)
Other	15 (13%)

Table 2. Physical Characteristics

	Mean	Range	SD	Number (percent)
Age (yr)	63	23–96	23	—
Weight (kg)	79	45–172	22	—
Height (cm)	169	144–196	10	—
Total patients	—	—	—	117
<60 yr old	—	—	—	38 (33)
men	—	—	—	76 (65)
women	—	—	—	41 (35)
ASA physical status				
I	—	—	—	11 (9.48)
II	—	—	—	33 (28.45)
III	—	—	—	64 (55.17)
IV	—	—	—	8 (6.9)

lon, Tract Medical, Jaffrey, New Jersey) catheter with the wire stylet withdrawn 2 cm was passed in a cephalad direction through the needle, which was then withdrawn, leaving 2–4 cm of catheter in the subarachnoid space.

Having established free flow of CSF through the catheter, small doses of one of the routinely used hyperbaric local anesthetic solutions for spinal anesthesia (e.g., tetracaine, 0.5%, or bupivacaine, 0.75%) were injected until an adequate level of anesthesia was reached. This was then maintained by injections of small doses of local anesthetic when the level of anesthesia had regressed by two segments, as determined by pinprick, or earlier if the patient complained of pain.

No vasopressors were given prophylactically and hypotension was managed, if and when it occurred, by intravenous fluids and by elevation of the patients' legs. Vasopressors (usually ephedrine 5 mg IV) were used if these measures were unsuccessful. The patients were, if indicated, sedated throughout the surgical procedure with incremental intravenous doses of midazolam (usually 1-mg doses) and/or fentanyl (25–50 μg doses).

The patients' ECGs, pulses, and blood pressures were monitored (intra-arterially, or by automated oscillometry) and recorded throughout the procedure. The number of attempts needed for dural puncture, the type of local anesthetic administered, the level of anesthesia as determined by pinprick, the onset time for adequate levels of surgical anesthesia, the duration of the surgical procedure, blood loss, the volume of IV fluid given, and any complications, such as difficulty in threading the catheter, bloody tap, or poor CSF flow from the catheter, were recorded.

Postoperatively the patients were visited by one of the authors on the first, third, and seventh postoperative days to record the incidence of PDPH and the times the patients were mobilized. If PDPH occurred, the patient was treated with bed rest, hydration, and an epidural "blood patch," if conservative treatment failed. Any patient discharged before the seventh day was contacted by telephone. Any patient complaining of PDPH after discharge was treated in our pain clinic.

A PDPH was defined as headache that appeared after spinal anesthesia, was posture dependent, occurred when the patient was upright and subsided when the patient lay down, with accompanying symptoms of nausea, vomiting, and/or photophobia. PDPH usually lasts for a day or more and may occur any time within the first 6 postoperative days, more commonly within the first 3 days (14). The patient must not have had this type of headache before surgery, and the headache must also have been documented in nursing notes.

Results

Details of each patient's age, sex, weight, height, and physical status are given in Table 2. Twenty-one patients had bupivacaine and 91 tetracaine anesthetics. The mean total doses of bupivacaine and tetracaine given were 20.4 ± 10.6 and 15.7 ± 7.7 mg, respectively. Six patients required general anesthesia because of inadequate anesthesia. Details of the complications encountered are given in Table 3.

The mean ± SD of the onset time for adequate level of surgical anesthesia (onset block time), duration of surgery, and time spinal catheter remained in the subarachnoid space were 13 ± 9, 215 ± 130, and 292 ± 152 min (excluding eight patients in whom the spinal catheter was left in situ overnight, where the time it remained there was greater than 1000 min), respectively. The mean upper level of sensory anesthesia was T-7 ± 2. Systolic blood pressure decreased from 140 ± 23 mm Hg to a minimum of 116 ± 22 mm Hg over a mean time of 16 min ± 13 during the onset of anesthesia. The mean time for patient mobilization was 1.5 ± 2 days. In 19% of the patients, two or more attempts were needed to locate the subarachnoid space. The mean intraoperative blood loss and IV fluid replacement were 484 ± 415 and 3015 ± 1797 ml respectively.

Table 3. Technical Complications

Type	Number of patients
Inadequate anesthesia	6 (5.1%)
Difficulty threading catheter	5 (4.3%)
Bloody tap	3 (2.6%)
Poor CSF flow	2 (1.7%)
None	101 (86.3%)

PDPH was detected in only one patient: a 29-yr-old man (weight, 100 kg; height, 190 cm) in whom the spinal anesthesia had been inadequate and general anesthesia was required. The spinal catheter was removed at the end of the procedure, remaining in the CSF for 120 min. He required treatment with an epidural blood patch for relief of his symptoms, which started on the third postoperative day. No signs of infection, neurological sequelae, or other complications of anesthesia were found in any of the patients.

Discussion

The incidence of PDPH after CSA was surprisingly low. In contrast, Carbaat and Crevel (15), in a prospective study of 100 patients whose mean age was 49 yr, reported PDPH in 37% after diagnostic lumbar puncture using an 18-gauge needle.

Previous retrospective studies, with the exception of that by Giuffrida et al. (16), have reported a low incidence of PDPH after CSA. Giuffrida et al. reported a 16% incidence of PDPH in 74 obstetric patients after cesarean section under CSA, despite the use of a 21-gauge needle and catheter. In contrast, our findings are in agreement with those reported by Peterson et al. (6), who found no patients with PDPH in a retrospective study of 52 consecutive cases of CSA, and with Kallos and Smith (7), who also reported no patients with PDPH in a study of 121 patients who underwent total hip replacement under CSA. In both of these studies (6,7), an 18-gauge Tuohy needle was used and the average age of the patients was comparable: the mean age in Peterson's study was 70, with ten patients younger than 60; in Kallos and Smith's study, the mean age was not given but 40% were younger than 60 yr old. The duration of surgery was slightly shorter in Peterson's study, 181 (60–410) min, than in ours. There was no mention in Kallos and Smith's paper of either the duration of surgery, the length of time the catheters remained in the CSF, or how the patients were followed up postoperatively, that is, retrospectively or prospectively.

Accepted teaching is that the incidence of PDPH increases with increasing needle diameter and decreases with patient age (14). Reports of the incidence of PDPH after single-injection techniques vary from 0.24 to 37% (10–15). In this study, the size of the spinal needle used was 18-gauge through which a 20-gauge catheter was passed, compared with the smaller needle sizes usually used—22 or 25 gauge in single-injection spinal anaesthesia. Thus one would have expected an increased incidence of headache in this study compared with studies in which a single-injection technique was used.

The low incidence of PDPH in the present study cannot be wholly explained by the older age of patients studied. The mean age of the patients in this study (63 yr) is similar to that in a recent study by Johnson et al. (13). They compared two groups of 112 patients each, mean age 69 ± 8 yr, undergoing total hip replacement under either single-injection spinal anesthesia using a 22-gauge needle or general anesthesia. In the spinal group, five of 112 patients developed PDPH, an incidence of 4.5%.

The effect of bed rest on the incidence of PDPH is controversial. However, in an elegant study (100 patients), Carbaat and Crevel found no statistical difference in the incidence of PDPH in two similar groups of 50 patients each who had lumbar punctures with 18-gauge needles, with patients in one group having no bed rest, and those in the other 24 hr bed rest (15). The mean ages were 47 and 51 and the incidence of PDPH was 38% and 36% in the two groups.

The relationship of the direction in which the bevel of the needle faced as it went through the dura may be significant. In a prospective study on the effect of needle bevel direction on the frequency of PDPH in 482 patients undergoing single-injection spinal anesthesia, Mihic found that the incidence was lower when the needle was inserted parallel to the longitudinal dural fibers than if it was at right angles to them (10). Ten of the first 62 patients (mean age 58) in Mihic's study in whom the bevel of the spinal needle (22 or 25 gauge) was inserted at right angles to the longitudinal dural fibers developed PDPH, an incidence of 16%. Among 420 patients (mean age 51) in whom the bevel of the needle (22 or 25 gauge) was parallel to the longitudinal dural fibers only one developed PDPH, an incidence of 0.24%. There were no other significant differences between the two groups.

The cause of PDPH is thought to be reduced intradural pressure after leakage of cerebrospinal fluid (CSF) out of a hole made in the dura that fails to close after dural puncture. Franksson and Gordh confirmed this in postmortem specimens from patients who had undergone dural puncture 2 weeks prior to their death (17).

The only difference between our group of patients

and those studied following single-injection spinal anesthesia, needle size notwithstanding, is the catheter in the subarachnoid space. Thus does the catheter itself reduce the incidence of PDPH? If it does, how?

After a large hole is made in the dura by an 18-gauge spinal needle, the catheter is passed through the needle into the subarachnoid space; the needle is then withdrawn, leaving the hole in the dura filled by the spinal catheter, thus minimizing CSF leakage into the epidural space. But what happens when the catheter is removed some hours later? One may postulate that an inflammatory reaction develops in the dura surrounding the puncture site, and that when the catheter is removed, edema or fibrinous exudate resulting from the inflammatory reaction seals the hole in the dura, thus preventing leakage of CSF. If so, one would then expect a low incidence of PDPH. Our hypothesis is supported by the recent experimental studies on cats by Yaksh et al. (18). They reported that microscopic examination of the dura in cats after implantation of subarachnoid catheters for 19–21 days revealed an inflammatory response with a thin fibrotic sleeve surrounding the catheters.

In summary, 117 patients who had surgery on the leg or lower abdomen under continuous spinal anesthesia were followed during the first postoperative week for postdural puncture headache (PDPH). Only one patient, a 29-yr-old man, developed PDPH. No other complications attributable to the anesthetic technique were found. We conclude that with a PDPH incidence of less than 1% and the possibility of safely controlling the level of anesthesia, continuous spinal anesthesia offers an excellent anesthetic method for long operations, particularly in elderly or severely ill patients.

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Use of Computed Tomography to Locate a Sheared Epidural Catheter

D. C. Moore, MD, A. A. Artru, MD, W. A. Kelly, MD, and D. Jenkins, MD

Shearing of plastic tubing when it is being inserted through a needle is a known hazard. If this occurs in association with epidural anesthesia, if the tubing is radiopaque, and if it is located by an anteriioposterior roentogenogram between the vertebra at the site of its insertion, it is usually *thought* that the sheared off segment lies in the epidural space (Fig. 1), and further localization is seldom undertaken. We report a case that fits the above scenario. However, further investigation revealed that the tubing was not in the epidural space.

Case Report

Placement of an epidural catheter was attempted in a 23-yr-old patient. Using the midline approach, an 18-g directional needle (Tuohy), the L-2 interspace, and the loss-of-resistance test (saline in the syringe) the bevel of the needle was thought to be in the epidural space. Air was injected through the needle believing it might facilitate passage of the plastic catheter into the epidural space. The wire stylet in the catheter was withdrawn so the tip of the stylet lay 3 cm from the tip of the catheter. The catheter was then passed through the needle but could not be inserted 3 cm beyond the tip of the needle. At that point, the catheter was unintentionally withdrawn from the needle. When the catheter emerged from the needle, 2 cm of it was missing. The Tuohy needle was withdrawn, the technique abandoned and general anesthesia was administered.

After the completion of surgery, the anteroposterior roentgenograph revealed a loop of catheter in what was presumed to be the epidural space (Fig. 1). However on closer examination, air was noted in the muscles lateral to the spinous processes of the lumbar vertebrae (Fig. 1). This combined with the difficulty in advancing the catheter made us suspicious as to the catheter's location. Therefore computed tomography (CT) seemed advisable. CT showed the catheter to be lateral to the spinous processes, posterior to their laminae, and in the multifidus muscle (Figs. 2,3).

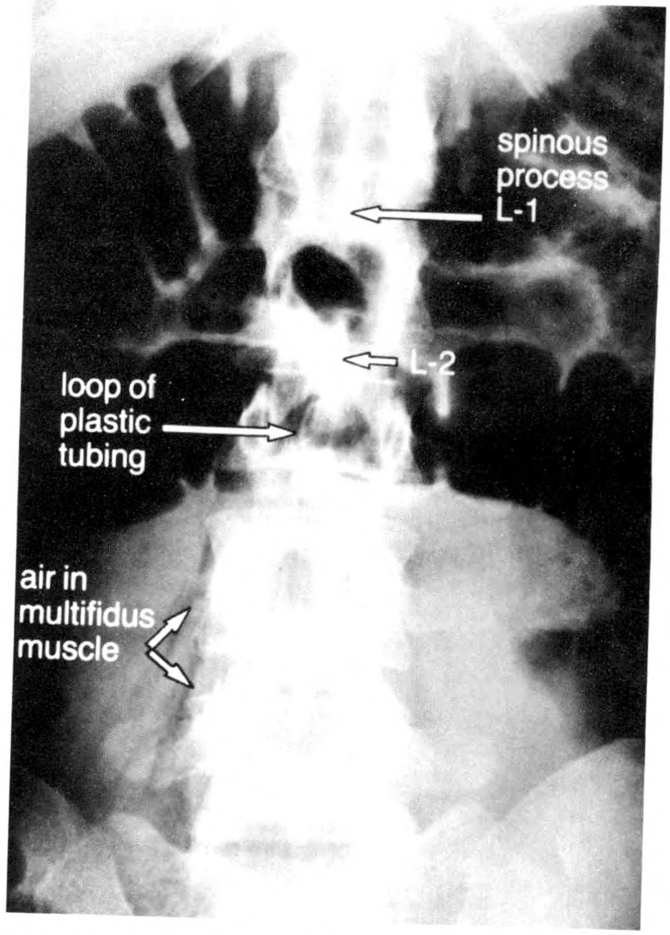

Figure 1. Anterioposterior roentogenogram showing sheared off radiopaque catheter at the L2–3 interspace and air in multifidus muscle.

Discussion

Regardless of whether or not plastic tubing used for catheters in regional anesthesia is radiopaque, the patient must be told if it is sheared off. In this case,

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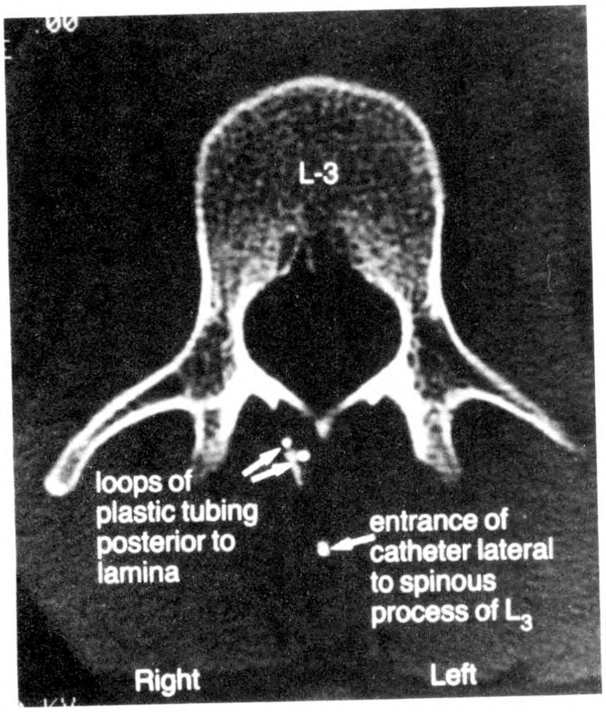

Figure 2. Localization by computed tomography of the plastic tubing lateral to the spinous process and posterior to the lamina of the vertebra.

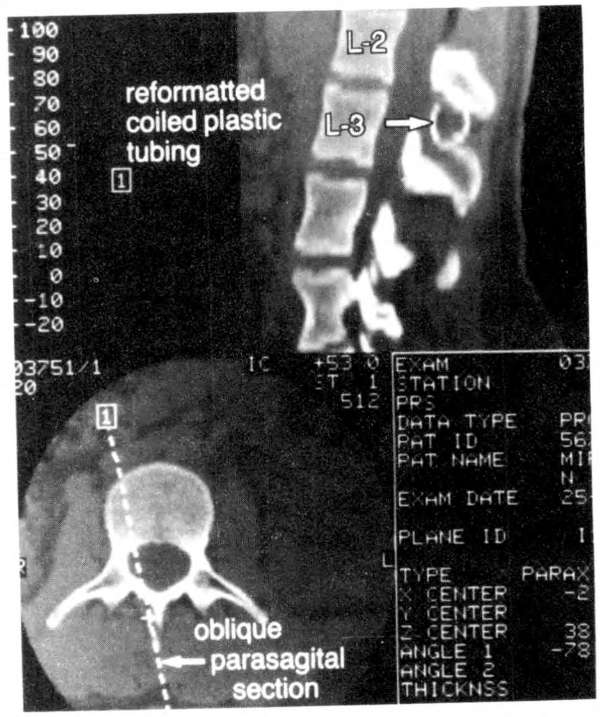

Figure 3. Computed tomography reformatting of the plastic tubing confirming its precise location lateral to the interspinous ligament of L2–3.

being radiopaque, precise location of it by CT was valuable because it permitted more explicit explanation to the patient of the risks of removal, the future assessment of any alleged complication (e.g., backache, infection), and precise location of the catheter should its removal become indicated. To date it has not been removed.

Respiratory Depression after Single Epidural Injection of Local Anesthetic and Morphine

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The use of epidural narcotics for postoperative analgesia is well-described and accepted. Whereas a variety of opioids have been used, morphine remains the most widely studied. The literature is replete with studies concerning morphine administration through an epidural catheter after general anesthesia or epidural regional block upon completion of surgery. Yet for operations in which repeated doses are unnecessary, single-injection epidural anesthesia is the method of choice, and epidural catheter placement, with its risk of associated morbidity, can be avoided. Single epidural injection of local anesthetic followed immediately by the epidural administration of a narcotic is a logical alternative for brief procedures in which prolonged postoperative analgesia is desired. This method requires a greater volume of injected solution than the typically described 5–10 ml of narcotic diluent and may be associated with more extensive epidural spread and a theoretical increased risk of side effects.

The recent study of Gürel et al. (1) described such a single-injection technique for anorectal surgery using prilocaine 2% (20 ml) and morphine (3 ml). They saw no evidence of respiratory depression in the 44 patients given epidural morphine, and concluded that "the single low dose of morphine eliminated the danger of early and delayed respiratory depression." That such a conclusive statement must be interpreted with caution is demonstrated by the present case report of a patient who developed bradypnea and somnolence after a single epidural injection of lidocaine with epinephrine and morphine. Treatment with naloxone effectively reversed the respiratory depression without affecting the level of analgesia.

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Case Report

A 24-yr-old, 180-cm woman was admitted for repair of an inguinal hernia. Her health was otherwise excellent, and she was nursing her 5-month-old infant. She reported a prior history of multiple drug abuse but had abstained for several years prior to this admission. Preoperative evaluation was negative except for frequent asymptomatic ventricular premature contractions noted on the electrocardiogram. The patient requested a minimal amount of anesthetic and postoperative narcotics in light of her breastfeeding and prior drug dependence. An epidural technique using local anesthetic and morphine was planned for the operation, which was expected to last less than 1 hr.

In the operating room, the epidural space at the fourth lumbar interspace was easily identified by the loss-of-resistance technique. A negative test dose of 2 ml lidocaine, 1.5% with epinephrine, 1:200,000, was followed by 25 ml of the same solution in 5-ml aliquots. After a negative aspiration test, preservative-free morphine, 5 mg in 5 ml, was subsequently injected via the same epidural needle. The sensory level of anesthesia reached approximately T-8 after 15 min. The surgery lasted 105 min, including anesthesia time, and was entirely uneventful. During the course of the procedure, the patient was given a total of 5 mg of IV midazolam. She remained comfortably sedated, responsive to commands, and vital signs were stable. The patient was admitted to the postanesthesia recovery room awake and with a respiratory rate of 20, blood pressure of 124/58 mm Hg, and pulse of 77 beats/min at 12:45 PM. It was noted at 1:15 PM that the patient was becoming drowsy, and at 1:20 PM she needed coaching in order to breathe at a rate greater than 4 breaths/min. At 1:30 PM naloxone, 0.4 mg, was given IV, oxygen was given by nasal cannula, and an apnea monitor was applied to the chest. By 1:45 PM respirations were 4–8 breaths/min with coaching, and the patient remained somnolent. A second IV injection of naloxone, 0.4 mg, was given, and a continuous naloxone infusion at the rate of 0.4 mg/hr was initi-

ated. The patient's respiratory rate and level of somnolence improved quickly, but at 2:45 PM both level of consciousness and respiratory rate decreased once again. A third IV bolus of naloxone, 0.4 mg, was given, and the naloxone infusion rate was increased to 0.6 mg/hr. The patient had no further respiratory depression or unusual somnolence, and was discharged to the ward where she was observed overnight with apnea and ECG monitors. The naloxone infusion was discontinued at 10:00 AM the next day, and the patient continued to have satisfactory analgesia without further episodes of bradypnea. She required no parenteral or oral analgesic medications throughout the 2-day hospitalization.

Discussion

Postoperative analgesia produced by epidural administration of opioids after abdominal surgery is superior to that produced by parenteral opioids (2), and offered two distinct advantages in this patient: avoidance of systemic doses of narcotics with breastfeeding; and the patient's history of drug abuse. A variety of epidural narcotics have been used successfully, but morphine remains the most widely studied. Administration of the narcotic is generally done at the completion of the surgical procedure using an epidural catheter. However, use of an epidural catheter may be associated with a significant rate of failure to place the catheter in the epidural space, as well as migration of the tip of the catheter into a vessel or the subarachnoid space, shearing of the catheter tip, patchy anesthesia, hematoma, infection, production of parasthesias, and other less common complications (3). For brief yet painful procedures such as in the present case in which an epidural opioid is desirable, a single-injection technique without catheter placement can provide sufficient intraoperative anesthesia and postoperative analgesia. In addition, administration of the morphine at the onset of such a procedure is desirable in order to avoid a nociceptive window as the local anesthetic sensory block regresses, as the onset of analgesia from epidural morphine is relatively slow.

Various factors are associated with an increased incidence of respiratory depression after epidural morphine, including advanced age, underlying respiratory insufficiency, concomitant use of parenteral opioids and sedatives, the addition of epinephrine to the injectate, and increased rostral CSF spread due to excessive narcotic dose or injected volume (4). Of these factors, the latter three may be applicable in this patient, who developed naloxone-reversible bradypnea and somnolence. The somnolence associated with such respiratory depression has been previously reported (5), and will not be discussed further except to note that it was repeatedly a harbinger of the bradypnea that followed within minutes.

Abnormally elevated rostral CSF morphine levels due strictly to a 5-mg dose is unlikely in this case, as this has been associated with a very low incidence of respiratory depression in numerous studies (4,6,7). Cousins and Mather have pointed out that one of the unanswered key issues regarding the pharmacodynamics of epidural opioids is the optimum volume of injectate (2). After epidural injection of morphine, a high concentration of the ionized drug is available to migrate to supraspinal structures. Whereas the actual morphine dose may be the critical factor responsible for spread of opioid effects into the brainstem, large volumes of injectate could enhance rostral migration. The majority of investigations in this field have employed epidural opioid injectate volumes of 10 ml or less. Diluent volumes as large as 20 ml have been used, with small but significant slowing of respiratory rate reported in one study (8). Gürel et al., using a volume of 23 ml to inject 3 mg of morphine, concluded that this dose and volume posed no danger of respiratory depression (1). The patient described herein received 27 ml of lidocaine and 5 ml of morphine solution for an effective injectate volume of 32 ml. Such a volume was indicated to provide an adequate level of operative anesthesia in this young, tall patient using a single-injection technique, yet was a likely etiology of excessive rostral morphine spread. It cannot be concluded that respiratory depression would have been induced by this large injected volume if the morphine dosage had been limited to the 3 mg used by Gürel et al.

Although the vasoconstrictor effect of epinephrine is desirable as a means to prolong and intensify the effect of epidural local anesthetics, reduced clearance of morphine from the epidural space can be associated with increased side effects. In this patient, the injectate contained 135 μg of epinephrine mixed with lidocaine, which may have enhanced the CSF peak concentration of the subsequently injected morphine. Bromage et al. reported more rapid rostral spread of morphine and marked worsening of respiratory depression with apneic spells due to the addition of 50 μg of epinephrine to 10 mg of epidural morphine, and suggested a reduction in epidural morphine dosage if epinephrine is used as an adjuvant (9). Such differences had not been observed in his earlier clinical study (10). Nordberg failed to show increased CSF uptake due to the addition of 50 μg of epinephrine to 2 mg of epidural morphine (11), yet more recently demonstrated higher peak CSF morphine concentrations after coadministration of epidural morphine with

epinephrine than after morphine alone (12). In their study of the effect of epinephrine on epidural opiate absorption, Jamous et al. used the lipophilic diacetylmorphine in order to make the effects of vasoconstriction maximally apparent (13). They demonstrated significantly reduced systemic absorption of diacetylmorphine with the addition of epinephrine, and an even greater reduction if the epinephrine was given as pretreatment 5 min prior to the epidural narcotic injection. Direct extrapolation of these results to the use of epinephrine with epidural morphine are uncertain, but the similarity in timing of drug administration between the epinephrine-pretreated group and the patient under consideration in this report is apparent—both demonstrated particularly slow systemic absorption and potentially elevated rostral opioid spread. Such conflicting data suggest that there is insufficient knowledge to guide the proper dose of vasoconstrictor as additives to epidural morphine solutions, and caution is advised.

The residual CNS-depressant effects of adjuvant anesthetic drugs is another factor said to contribute to delayed respiratory depression. In addition to the epidural medications, the patient in this case report was given 5 mg of midazolam approximately 2 hr prior to the onset of the bradypnea. This may have contributed in a minor way to the observed respiratory depression, as midazolam has been described to have such an effect in combination with parenteral narcotics (14).

In conclusion: 1) The single-injection technique of epidural local anesthetic with morphine as described by Gürel et al. (1) may be appropriate for short procedures associated with significant postoperative pain. 2) Conventional volumes of epidural local anesthetic diluent (20 ml or greater) may be associated with an elevated risk of rostral CSF spread of concomitantly injected morphine. The safety of such injectates with a volume of greater than 20 ml has not been shown and should be used with great caution pending further study. 3) The usual dose of epinephrine used with epidural local anesthetic (100 μg or more) may contribute to subsequent respiratory depression and should be used in the lowest necessary dose, if at all.

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Letters to the Editor

Transatlantic Lessons: One Man's View

To the Editor:

It has been said that Great Britain and the United States are two countries divided by a common language. The same may well be said to be true of anesthetic (or should it be anaesthetic?) practice between the two countries: we talk the same language but practice differently. This letter is intended to describe some of the lessons that I have learned from practicing anesthesiology in the United States and, perhaps, to point out some of the lessons that could be learned from traffic in the other direction. It is written from the point of view of an academic from a British university working in an equivalent institution in the United States. As such, it necessarily represents one man's view and is biased toward two particular institutions. Two things that are reassuring are that drugs and anesthetic techniques used are comparable between the two countries.

One major difference between the two countries is the residency program. The American resident, having completed 3 years postintern training, possibly never having given an anesthetic completely on his own or having achieved no formal academic postgraduate qualification apart from a single multiple choice paper, may set up in private practice and, henceforth, work without further supervision. His British counterpart will undertake a training that is a minimum of 6 years. During training he will work increasingly on his own, during the first year undertaking less complicated procedures until in the final years, it would be expected that a senior registrar undertake major anesthetic cases without direct supervision. Although no system is perfect and the British training appears excessively long, postgraduate examinations ensure a minimum knowledge base, and the clinically incompetent resident will find that he cannot progress up the training ladder. It has been suggested to me that junior faculty posts in American universities are equivalent to senior registrar positions, but there is no formal assessment in these positions, nor are they obligatory. It has further been suggested to me that medico-legal and economic considerations prevent residents working on their own. I fail to understand an insurance system that demands supervision of a trainee at all technical levels on June 30, but no further supervision on July 1. The British trainee is able to spend up to a year of his training in an approved post in another country and many have learned a great deal from this time. Several American Universities provide 1-year posts for British senior registrars; perhaps more exchange posts could be offered in British universities and "cross-fertilization" encouraged.

The anesthetic machines and monitors are different in the USA, and I have learnt a lot from their use. Why British machines do not have a lock to prevent hypoxic mixtures being administered is something I do not understand. I had always wondered why my American colleagues used smaller doses of muscle relaxants than I did. The answer is obvious: routine monitoring of neuromuscular transmission (seldom carried out in Britain) leads to more judicious use of neuromuscular blocking agents. My American experience has also firmly convinced me of the value of the noninvasive techniques of continuous monitoring via an esophageal stethescope and pulse oximetry, techniques seldom used in Britain. I have also learned from the use of "high-tech" monitoring facilities, generally unavailable in the UK because of cost, such as transesophageal echocardiography and pulmonary artery oximetry. However, an American could learn much from his British colleague with respect to contact with the actual patient. I have seen patients in the United States with eyes covered by plastic tape to protect against the ultraviolet lights and then the head placed in a plastic bag to prevent heat loss; the patient vanishes. I seldom see the United States residents palpate the pulse, examine the conjunctiva, feel the skin, or look at the pupil.

There is also a difference between the two countries in the relationship between surgeons and anesthesiologists. In Great Britain, the consultant (attending) works with specific surgeons on specific days of the week, thus allowing rapport and mutual respect to develop. There are no CRNAs in Britain; the situation where a physician attends in more than one room does not therefore arise. In many of the institutions I have visited in the US, anesthesia is treated as a technical support specialty. Never in Britain have I heard the bald command "Anesthesia-table up!". Although it may be anathema to American hospitals, I am sure that a faculty social club and bar, such as exists in most British hospitals, would do much to promote interspecialty relationships.

The dollar appears all-important in American medical practice and can interfere with patient care. After a local standby case (a euphemism for neuroleptanalgesia), I was curtly informed by the surgeon that the patient could not go to the recovery room, as the surgeon had informed the patient that he would not incur the cost thereof. Patients in the United States also require more detailed explanations

and are generally better informed than their British counterparts. This is perhaps because they are paying more directly for their care. In addition, much has been written about the litigious nature of American medicine and the high cost of malpractice insurance. My British malpractice insurance costs approximately $400 for unlimited cover worldwide (with the exception of the US), whereas American coverage is approaching $100,000 in some states. Obviously there is something seriously wrong with such a system. In the long run, neither the patient nor the physician will benefit from such high insurance costs.

In view of the amount of money spent on health care in the US, I am surprised that consumers accept nurse anesthetists and do not demand physician anesthesia. The CRNAs with whom I have worked generally provide excellent care, but they do not have the same clinical background as a physician. I admit to some bias coming from a system where only physician anesthesia is available, but why are there no nurse surgeons? Why couldn't a nurse surgeon graft coronary arteries (under physician direction) while a CRNA administers the anesthetic?

Another area where money is important is in the area of research. Although American researchers may bemoan the reduced availability of the National Institutes of Health and other sources of research funds, to the British investigator the United States still seems a land flowing with milk and honey. There are severe restrictions on research funding in the UK, partly as a result of government policy and partly as a result of retrenchment by the pharmaceutical industry. Yet Great Britain still continues to be productive in research in both basic sciences and clinical medicine. Perhaps the lack of money concentrates the mind. If American researchers think things are getting bad, to put it in the words of an ex-movie star turned politician; "You ain't seen nothing yet."

All the British physicians I know who have worked in the United States have found it valuable experience. I am certain that Americans traveling in the other direction also would learn a lot. The necessary posts would be easy to set up by exchange arrangements rather than the current one-way traffic. Unfortunately, I understand that the American Board of Anesthesiology does not permit such exchange programs, although individual trainees may petition the board for approval of a period of time spent abroad. Like the British trainee taking a post in the US, an American trainee taking an exchange post in Great Britain would derive significant benefit, and anesthesiology as a specialty would benefit from this cross-fertilization.

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The Work of Breathing

Editor's Note: The following reply to Dr. Ehrenworth's letter was inadvertently omitted from the March 1987 issue.

To the Editor:

This is in response to the letter written by Dr. Jan Ehrenworth (1987;66:285–6) regarding our paper, "The extra work of breathing through adult endotracheal tubes," (1986;65:853–9). We are very pleased that Dr. Ehrenworth read our paper with such obvious interest.

We must disagree with Dr. Ehrenworth's statement, "The authors state that their data support the fact that the insertion of an 8.00-mm endotracheal tube will double the work of breathing." We were, in fact, cautious to state that "such an interpretation must be made with caution," pointing out that "the endotracheal tube does not simply increase resistance, and hence work; it replaces the upper airway resistance." Indeed, a measurement of the normal work of breathing was not the essential subject of our paper. Nonetheless, we must remind Dr. Ehrenworth that he should take into account the fact that the contribution made to the total work of breathing by that part of the airway replaced by the endotracheal tube does not constitute the whole work of breathing, for it does not take into account the work required to overcome the resistance to air flow in the other airways, nor the work required to overcome inertial and elastic forces. It is not unreasonable, therefore, to argue that the work required to breath through that part of the airway replaced by the endotracheal tube is only a small component of the total work of breathing. Intubation with a size 8 tube using the conditions of ventilation described in our paper could, therefore, be expected to increase the work of breathing. However, it was not the purpose of our study to examine the work of breathing but rather to establish that work was a better measurement for the comparison of endotracheal tubes of different sizes than resistance to flow, and we feel that our data justified our conclusion, ". . . that for comparison of endotracheal tubes of different sizes work is a more appropriate measurement than resistance."

We are, however, indebted to Dr. Ehrenworth for identifying an error in the labeling of our graph in Figure 3. The abscissa should, of course, have been labeled r, as he points out, and not 1/r.

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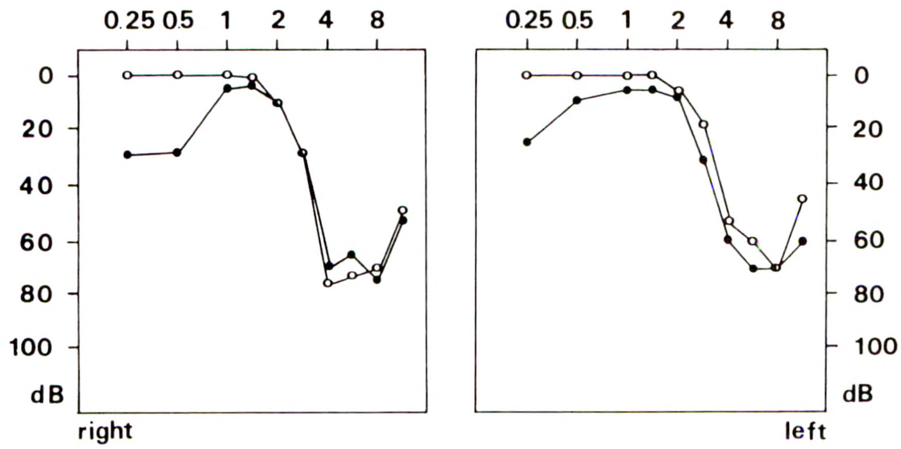

Figure 1. Bilateral hearing loss in the low frequency range. Closed circles, audiogram 48 hr after spinal anesthesia; Open circles, second audiogram 12 days later.

Hearing Loss After Spinal Anesthesia

To the Editor:

We read with interest the report by Lee et al. of unilateral hearing loss for 4 days after spinal anesthesia (1). We observed a similar case that lead to a prospective study (2), in 100 urologic patients, that showed eight cases of auditory disturbances after spinal anesthesia. Because they were very transient we were able to obtain audiograms in only three patients. The findings in these three cases were similar to those shown in the figure. In our experience this complication usually needs no special therapy. Parenthetically, hearing disturbances after spinal anesthesia were mentioned in 1914 by Terrien and Prélat (3).

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Wakefulness during Cesarean Section

To the Editor:

Only one fairly basic message can be gleaned from the report by Dr. Schultetus et al. (Schultetus RR, Hill CR, Dharamraj CM, Banner TE, Berman LS. Wakefulness during cesarean section after anesthetic induction with ketamine, thiopental, or ketamine and thiopental combined. Anesth Analg 1986;65:723–8.): the anesthetist should ensure that his patient is actually unconscious before administering a relaxant, passing an endotracheal tube, and permitting the start of surgery.

I cannot credit that the patients who "followed commands" within 1 min after receipt of thiopental had ever truly lost consciousness. Your contributors do not state whether or not they sought a response. My old-fashioned method is to have the patient count out loud, at roughly one a second, while I inject the induction drug, and I continue injecting until the patient has obviously lost consciousness. With thiopental, they usually count to between 15 and 20. Recently I anesthetized a woman who was neither obese or addicted to alcohol or other drugs—for an elective cesarean section. She counted to 74 and had received 450 mg thiopental before she fell asleep. She had come to us from overseas for her anesthetic, having been aware during two previous sections conducted in her home country. The legitimate inference is that on the previous occasions the anesthetists had, like your contributors, administered a "standard dose" of induction agent and assumed that she has been rendered unconscious.

Has all sense of realism in the art of anesthesia been lost? The study by Schultetus et al. has not shown that awareness is more likely to occur when thiopental is used than when ketamine is administered; it has simply shown that the basic rules of anesthetic practice were flouted.

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In Response:

Of the 12 patients who followed commands during anesthesia, four did so beginning 1 min after induction of anesthesia. Although it is possible that these four early responders never lost consciousness, in each instance the patient closed her eyes, became apneic, and did not struggle during the onset of paralysis. These signs resembled those

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exhibited by the other 32 patients who either did not respond to commands or who did so later. However, we did not begin testing for awareness until 1 min after anesthesia was induced and therefore cannot determine with certainty whether the patients awakened early or never lost consciousness.

The dose of thiopental we chose for induction (4 mg/kg) is recommended (1), is widely used, and has been used in other studies (2). The average patient in the thiopental group weighed 78.9 kg. Thus the average dose of thiopental was 316 mg, which is slightly greater than that previously recommended for induction by Dr. Crawford (3).

Dr. Crawford describes his method of having the patient count aloud while he slowly injects thiopental. In the case he relates, the rate of injection was 6 mg/sec. If this is his usual practice and if most patients count to 20 before losing consciousness, then he administers an average induction dose of approximately 120 mg of thiopental; much less than that used in our study. He further implies that his technique would result in a lower incidence of early awareness, a contention which has yet to be proven experimentally. On the contrary, his technique may result in lower peak levels of thiopental in the brain, which, through the redistribution of thiopental, would result in earlier awakening than would occur after a bolus injection of 4 mg/kg.

The real issue is how to reduce maternal awareness (if this is desirable) without adversely affecting neonatal outcome. Toward this end, our study demonstrates that the use of ketamine (1 mg/kg) for induction reduces the incidence of early intraoperative awareness when compared with thiopental alone (4 mg/kg) or in combination with ketamine (thiopental, 2 mg/kg, plus ketamine, 0.5 mg/kg). Whether thiopental administered by other techniques or in other dosages will reduce awareness is untested, as are many other drugs and drug combinations. Rather than assuming that all intraoperative awareness is caused by poor technique, studies should be conducted to identify those techniques and agents that correlate with a high incidence of awareness and to develop techniques that both reduce the incidence of awareness and achieve the goals of obstetric anesthesia.

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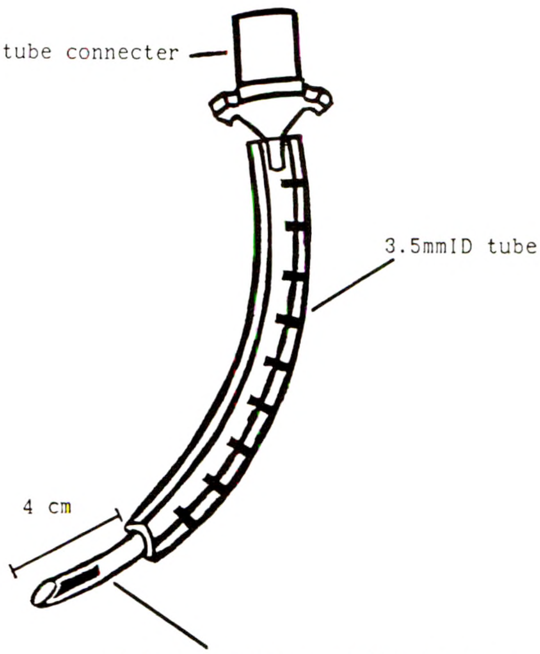

Figure 1. Kink-proof 2.5-mm ID endotracheal tube. A 2.5-mm ID tube is covered by a 3.5-mm ID tube, leaving distal 4 cm of 2.5-mm ID tube uncovered.

A Simple Method for Preventing Kinking of 2.5-mm ID Endotracheal Tubes

To the Editor:

Kinking of endotracheal tubes is an ever present threat in anesthesia, especially in pediatric anesthesia for neurosurgery, eye surgery, oral surgery, and ENT surgery. One solution is to use preformed endotracheal tubes such as the Oxford tube, the RAE tube (1), or the CAT tube (2). The smallest size of these tubes is 3.0 mm inner diameter (ID). However, premature babies require that 2.5-mm ID endotracheal tubes be used in these operations.

A simple method for preventing kinking of 2.5-mm ID standard tubes is to cut a disposable 3.5-mm ID tube 4 cm from the distal end. The 2.5-mm ID Portex tube (3.4 mm outer diameter, OD is then inserted through this 3.5-mm ID tube, leaving the distal 4 cm of the 2.5-mm ID tube uncovered. The end of the 2.5-mm tube into which a connector is to be placed can be cut at the length desired (Fig. 1). When this tube is inserted into the patient, kinking of the tube above the larynx is prevented, and the 3.5-mm ID tube ends just above the larynx, with only the 2.5-mm ID tube going between the cords. One must be careful not to insert the tube too deeply, as the 3.5-mm tube may damage the cord, as may happen with Cole tubes (3). Depth of

insertion is confirmed by the centimeter markings along the length of the tube.

We have used this method in over 20 cases and found it to be a simple, effective, and inexpensive means of preventing kinking of 2.5-mm ID endotracheal tubes in premature neonates.

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Animal Models of Hepatic Injury Associated with Halogenated Anesthetics

To the Editor:

The exchange between Gelman and Lind et al. (Anesth Analg 1986;65:545–7) raised some issues pertinent to possible metabolite mediated or direct hypoxic mechanisms in the "mildly hypoxic" and "markedly hypoxic" rat models. These models may not be the same. We write to add four important pieces of information supporting a role for reductive metabolism in the mildly hypoxic model.

1. Inhibition of reductive metabolism by cimetidine ameliorates the hepatotoxicity of halothane (1).
2. Selective induction of the oxidative pathway by isoniazid does not influence halothane hepatotoxicity (2), whereas selective induction of the reductive pathway by pregnenolone-16-α carbonitrile promotes liver injury (3).
3. The time course of onset of initial damage at 1–12 hr, maximal damage at 24–48 hr, and duration of damage 5–15 days is in keeping with metabolite mediated toxicity (4).
4. Exposure of phenobarbital-pretreated rats to halothane at 10 or 14% oxygen results in marked decreases in cytochrome P-450 content and associated metabolism of model substrates. Halothane administration in the absence of phenobarbital or during hypoxia (10 or 14% oxygen) does not result in changes in hepatic mixed function oxidase activity or hepatotoxicity. Hepatic necrosis was associated only with combinations of halothane and/or 14 or 10% oxygen and phenobarbital (5).

There can be no doubt that global and regional oxygenation of the liver are important factors contributing to halothane-induced liver injury in the mildly hypoxic rat model, as they are in the markedly hypoxic rat model. However, it is clear that other factors, including the formation of toxic halothane metabolites, are important in the mildly hypoxic rat model.

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Book Reviews

Neurological and Psychological Complications of Surgery and Anesthesia

B. J. Hindman, ed. Boston: Little Brown and Co., 1986, 284 pp, $18.00.

This volume in the respected IAC series is a watershed for anesthesia. It succeeds as the first attempt to integrate psychology and neurology into anesthesia. As an edited compilation it suffers from some unevenness. Yet as the handbook is organized, a melding of the psychology of anesthesia with its neurology, the volume succeeds as a well-edited treatise. It is a treasure trove of potential clinical studies and applications; it points to further areas which hopefully will be carved out in the coming years.

There is a breadth of topics covered which will appeal to all anesthesiologists interested in the following areas: awareness, postoperative delirium and anesthesia, intra- and extracellular chemistry of injured brain tissue, neuropathies, vascular disease and CNS events, and the psychologic/neurologic complications of cardiac anesthesia. Also included are functional evaluations of recovery from outpatient anesthesia, neuropathies and legal duty, regional techniques, and two chapters on preoperative preparation with children and with adults. There's something for everyone, and the other chapters are added bonuses on new territories in anesthesia.

One interesting aspect of the book is that theory is refreshingly present. While descriptive and explanatory topics are included, the inclusion of central chapters on psychologic processes which are disrupted by anesthetics allows the reader to ponder puzzles of mind and brain function more clearly than have previous efforts in the anesthesia literature. This must be a welcome sign to those seeking a general theory of anesthesia.

For example, the chapter on delirium and anesthesia describes and organizes syndromes observed daily in the recovery room. Treatment, especially preventative treatment, generally seems a long way off, but the authors urge some simple preliminary steps which are within reach. The excellent chapter on pediatric patient psychology describes how stages of a child's life can be incorporated into managing the preanesthetic period and emphasizes that sound principles of behavioral intervention are behind the efforts of a successful anesthetic with children.

In the area of preparation for surgery, no name stands higher in anesthesia than Egbert and his two patient preparation studies. The reader familiar with the quality of the previous work is disappointed by the effort here if only because so little progress has been made. However, Egbert does not provide a thorough review of the field but simply describes his clinical milieu. In the past 25 years there have been many studies examining the issue of preparation for surgery scattered throughout the disciplines of anesthesiology, psychology, and in the use of instructions and suggestions, with and without hypnosis. Egbert emphasizes that the medications delivered by anesthesiologists are so potent that the evaluation by the patient will in large part determine the response, whether to sedatives, narcotics, or inhalational agents. To this point the literature not reviewed by Egbert certainly concurs.

In marked contrast to the Egbert chapter, the chapter "Awareness and Recall" presents a relatively complete psychology of these central topics to anestheisia. The excellent writing style describes the different terms which on face value seem so obvious, "consciousness," "memory," "recall," and "awareness," and calls for precision in the use of these terms for the sciences of anesthesia and of psychology. When coupled with reports of purely technically inadequate anesthetics, postanesthetic awareness reports reveal a curious anomaly of anesthesia: anesthesia induces a state of unconsciousness but has no monitor of the presence or absence of this state. Awareness episodes occur particularly often in trauma patients, but the chapter does not cover this literature. Dr. Guerra has presented a cogent and realistic view of some of the factors associated with awareness episodes which are later postanesthetically recalled.

The neurologic injury chapters of the IAC volume are consistent with the theme of the volume. These descriptions are especially interesting because they bring structural considerations into the picture. The relationship of reticular, limbic, hippocampal, temporal and frontal structures with regard to functions such as memory, consciousness, and receptor functioning are not discussed. The descriptions of intra- and extracellular changes during cerebral injury are particularly well-written in a fluid style. The discussion of perioperative stroke by Hindman is well-organized with basic considerations of pathophysiology complemented by an overview of the evolving and controversial area of "cerebral protection." The author attempts to translate these concepts into useful clinical guides for preoperative evaluation and intraoperative management. Thorough referencing

makes this chapter a useful resource for pinpointing the recent literature on this topic.

The two subsequent chapters address the topic of neurologic complications of carotid endarterectomy, abdominal and thoracic aortic reconstructive surgery, and cardiac surgery. These chapters give well-presented and informative discussions of the incidence and mechanisms of neurologic dysfunction during these anesthetics. However, they fall short of a comprehensive review. Notably lacking is a detailed review of the EEG versus other modalities for the detection of cerebral dysfunction during anesthesia. Furthermore, the type of cerebral protection examined in the chapter on perioperative stroke by Pamela Shaw certainly deserves further elaboration. On the other hand, Shaw discusses functional evaluation of the nervous system through somatosensory evoked potential studies in prevention of ischemic damage to the spinal cord and suggests that online measurement of the nervous system's level of functioning be available in a useful form during operation.

The topic of compression neuropathy is covered in a simple yet complete fashion with case examples resulting in legal action providing a unique insight. While not a definitive review, this chapter provides useful lessons in compression neuropathies as they related to anesthesia along with the medical and legal implications which result. The reader is left convinced of the need for detailed anesthetic records addressing patient positioning as well as vigilance of all pressure points. In this sense, the chapter would benefit the beginning resident as well as the experienced physician seeking a brief review of this important area. Finally, Dr. Vandam presents a brief discussion of neurologic complications associated with spinal and epidural anesthesia. Again, the chapter provides an overview of this topic reflecting Dr. Vandam's substantial personal background in this area. The chapter is a highly readable and refreshing discussion.

In summary, the volume from IAC under the editorial supervision of Bradley J. Hindman of Beth Israel Hospital and Harvard Medical School can only be described as excellent and enlightening reading for the student and practitioner of anesthesia, psychology, and the brain sciences.

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Anesthesia for Obstetrics

Sol M. Shnider and Gershon Levinson, eds. Baltimore: Williams and Wilkins, 1987, 566 pp, $69.95.

This multiauthored text is the second edition of a popular and widely accepted reference and standard textbook that was originally published in 1979, and required considerable updating. The editors, together with 26 authorities in the fields of anesthesiology, obstetrics, neonatology and law have provided a current review of: 1) anesthesia for vaginal delivery and cesarean section, 2) anesthesia for complicated and high-risk pregnancy, 3) anesthetic considerations for nonobstetric disorders during pregnancy, and 4) the evaluation and resuscitation of the fetus and neonate. The primary orientation of this textbook is to the clinical practitioner and particularly to the resident physician training in anesthesiology. It also should prove particularly helpful to a variety of health care providers to pregnant women such as Lamaze instructors and labor and delivery room nurse practitioners.

Since the original publication of the first edition in 1979, numerous changes and advances have occurred in the specialty of obstetric anesthesiology. Consequently, the second edition has been significantly revised and rewritten, with a variety of new chapters added. Under the topic of local anesthetics in obstetrics, the editors have identified an important topic relating to controversies in selecting an appropriate drug, i.e., bupivacaine, chloroprocaine, or lidocaine. Within the section of obstetric complications, there are new chapters on anesthesia for the pregnant patient with asthma, diabetes mellitus, intracranial lesions, neuromuscular disease, morbid obesity and immunologic disorders—all complications not infrequently encountered in clinical practice. In addition, there are new chapters devoted to the use of intraspinal opiates, preterm labor, anesthesia for postpartum sterilization, amniotic fluid embolism, anesthesia-related maternal mortality, and fetal surgery. In all, a total of 13 new chapters and 11 new contributors have been added. The present textbook of *Obstetric Anesthesia* is probably the most all-inclusive reference with current bibliography in the English language as of 1987.

With few exceptions, most of the chapters from the 1979 edition have had major revisions. All chapters have been well-illustrated with a liberal supply of graphics and references updated to the time of publication. This reviewer was particularly impressed with the material presented in the following chapters: chapter 2, "Obstetric Anesthesia and Uterine Blood Flow"; chapter 10, "Intraspinal Opiates in Obstetrics"; chapter 17, "Anesthetic Considerations in Preeclampsia—Eclampsia"; chapter 25, "Anesthesia—Related Maternal Mortality"; chapter 28, "Anesthesia for the Pregnant Patient with Asthma"; and, chapter 29, "Anesthesia for the Pregnant Diabetic Patient."

The anesthesia resident-in-training and the practicing clinical anesthesiologist will find this textbook an excellent resource for information regarding the anesthetic management of both low-risk and high-risk parturients, and for clinical problems relating to the fetus at risk.

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Primary Anesthesia

Maurice King, ed. Oxford, UK: Oxford University Press, 1986, 169 pp, $13.95.

Imagine for a moment that you are a general practitioner at a remote rural hospital. Lacking an anesthesiologist, the

medical director has appointed you to provide anesthetic services for your surgical colleagues. Available to you are a limited selection of local anesthetics for regional block and major conduction anesthesia, with appropriate nondisposable needles. Intravenous agents are pentothal and ketamine; inhalational agents are delivered via a draw-over vaporizer with air as the carrier gas. Oxygen must be carefully conserved, and nitrous oxide, expensive and erratic in supply, is not a reliable resource. The limits of monitoring are a precordial stethoscope, a blood pressure cuff, and a finger on an easily palpable artery. There is no ventilator. The responsibility for maintaining equipment, recycling supplies and ordering drugs is yours. A vignette drawn from bygone days in anesthesia? In the rural Third World, it is a recurrent scenario. Anesthesiologists are few, surgical cases are many, and resources are limited: primary care physicians are challenged to provide an acceptable minimum standard of anesthesia to all patients.

Primary Anaesthesia addresses this need. It is written for general duty doctors in rural hospitals of the developing world to improve anesthesia care when it is least adequate, using safe, simple, cost-effective methods. The contributors speak from extensive field experience in India and Africa, about which many have previously published. This book is the sophisticated successor to Bouton's chapter, "Anaesthesia and Resuscitation in Difficult Environments" in *Advances in Anaesthesia* (1975), Farman's *Anaesthesia and the EMO System*, and the *Machame Anaesthesia Notebook* of Kamm and Graf-Bannerman.

The text begins at "ground zero," discussing in practical terms the logistics and economics of third world anesthesia, providing a comprehensive inventory of equipment and drugs necessary and promoting safe practice principles, codified into "ten golden rules" for disaster prevention. Perioperative monitoring practice emphasizes vigilant inspection, palpation, and auscultation in theaters devoid of automated devices. Local anesthesia in all its applications assumes a prominent role in settings where the surgeon and anesthetist may be one and the same. Some techniques which would be poorly received in developed countries (e.g., cesarean under saddle block with local infiltration) are recommended here for their safety in the hands of a single operator under difficult conditions. Similarly, ketamine enjoys much wider application. The use of this drug as a sole anesthetic agent is clearly described, with techniques to minimize its risk and extend its limitations. Throughout the Third World, the shortage of compressed gases renders delivery of general anesthesia with a Boyle's machine expensive and often impossible. A draw-over vaporizer system using air as the carrier gas (supplemented with low-flow oxygen when indicated) is a safe, economic alternative. One comprehensive chaper details the equipment and techniques available for delivery of halothane, ether and trichloroethylene. Muscle relaxants and fluid therapy receive thorough attention, and an additional appendix outlines the steps for in-hospital production of intravenous solutions.

The principles of safe anesthesia practice consume the first two thirds of this book. The remaining third focuses on specific clinical problems (full stomach, hypovolemic shock, chronic medical disease, unusual surgical positions) and patients (obstetric, pediatric, maxillofacial, ophthalmologic). For the hospital with greater resources, guidelines are offered for the set-up and staffing of an intensive care unit. Safe practice standards are reinforced in the closing chapter on quality assurance in anesthesia. This modest volume is a singular contribution to anesthetic practice in the rural Third World and achieves the goals targeted in the preface by means of succinct text, illustrative case studies, self-test exercises, graphs, and line drawings. Some readers may take exception to the small typeface, the brief pediatrics section, and the absence of discussion (acknowledged by the author) on malignant hyperthermia. Overall, however, the text succeeds in presenting "anaesthetics that two-thirds of the world's people would consider themselves fortunate to have."

Western anesthesiologists seeking the challenge of practice in the bush will find this a packable and useful companion. For armchair travelers at home in their streamlined operating suites, *Primary Anaesthesia* brings a different perspective to the land of plenty.

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Advances in Anesthesia, volume 1

T. J. Gallagher, ed. Chicago: Yearbook Medical Publishers, 1984, 444 pp, $55.95.

Annual reviews and "clinics-type" publications are hybrids, combining the timeliness of a journal with the breadth of a text. However, despite their apparent advantages, these publications come and go. My shelves, and likely yours too, are filled with past volumes of now defunct series as well as others still being published; the mail brings announcement of new hybrids yet to come.

So what does one do with a monthly series from 1977, *Current Problems in Anesthesia and Critical Care Medicine*, which did not even complete its first full year of publication? Year Book Publishers and T. J. Gallagher, MD, the editor, have taken most of the topics and authors from the original (as well as added three new topics), revised and expanded the material and published them, phoenix-like, as Volume I in a new series, *Advances in Anesthesia*.

The topics and articles in the original were pertinent, authoritative, complete and well-edited; in their reborn state they still are. Subjects include respiratory failure, monitoring, nutrition, trauma assessment, renal failure, hypertension (systemic and intracranial), sickle-cell disease, and finally, anesthesia for healthy children—enough to tempt even the most specialized practitioner.

By now, Volume 1 has been succeeded by Volumes 2, 3, and 4. Editorship too has expanded, but the range of topics remains useful and appealing, the writing clear and authoritative. Let us wish this series a well-deserved long life.

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Closed-Circuit System and Other Innovations in Anesthesia

R. Droh and R. Spintge, eds. New York: Springer-Verlag, 1986, 253 pp, $54.29.

The Second International Symposium on Innovations and Management, Technology, and Pharmacology was held in Lüdenscheid, West Germany, in May 1984. This book is a collection of papers presented at the meeting by anesthesiologists, physiologists, pharmacologists, internists, and engineers. Although the symposium occurred 3 years ago, much of the material is current because it focused on new and innovative ideas at that time.

As the title suggests, much of the text is devoted to closed circuit anesthesia, and this subject is addressed in the first of four sections in the book. A chapter by Wallroth describes the technical conception of a semiautomatic anesthesia delivery system being developed by Dräger Manufacturing that will facilitate the introduction and lead to further technologic advancement of closed circuit anesthesia. A completely computerized, on-demand closed circuit ventilator, the Narcocon, is described by Spintge. Droh reports the delivery of over 60,000 closed circuit anesthetics at the Institute of Anesthesiology in Groningen, The Netherlands, during the past 12 years. Other authors report successful use of the method in cardiovascular, pediatric, and obstetric anesthesia. Unfortunately, some writers in this section encourage the use of closed circuit only by recounting clinical experiences, without the support of adequate data.

Noninvasive monitoring is treated in a section highlighted by Dorlas's chapter describing a continuous noninvasive blood pressure measurement using finger photoelectric plethysmography. The resultant device, Finapres, is now marketed in Europe and the United States by Ohmeda. This section features $tcpO_2$ and $tcpCO_2$ data in patients with normal and compromised circulation. Significant variations from arterial values, especially during periods of hypoperfusion, do not dissuade R. Lemke from pointing out the value of noninvasive continuous monitoring, although his study shows that accurate values could not be obtained without discontinuous invasive blood gas measurements.

In a third section, dealing with respiration and circulation, Klein reports stroma-free hemoglobin studies during extreme hemodilution, showing no significant alterations in blood lactate, glucose, free fatty acids, triglycerides, electrolytes or creatinine. He concludes that this type of oxygen-carrying colloid shows hemodynamic stability and remarkable metabolic compatibility in the animal studies.

Pharmacology is the subject of a brief final section including an interesting chapter by Chrusabik. He describes a patient-administered, on-demand, low-dose epidural morphine for postoperative pain relief. Patients did better when an initial bolus was injected, and neither accumulation nor tachyphylaxis were found with morphine.

Readers may consider the title of this book a misnomer knowing, as they do, that closed circuit anesthesia is not an innovation; but was used by John Snow in the nineteenth century, further developed by Ralph Waters in the 1920s, and widely used during the cyclopropane era of the 1950s. The editors too are aware of this and emphasize that at the present time, "the large-scale introduction of the closed circuit system has to be the occasion of completely new quality standards both in anesthesia and in all related technological sectors . . ."

Perhaps the most intriguing feature of this publication is found in the discussions reported at the end of each section. Presenters and participants raise important critical questions and issues as they consider how innovations in method and technology may relate to practical perspectives for the entire specialty.

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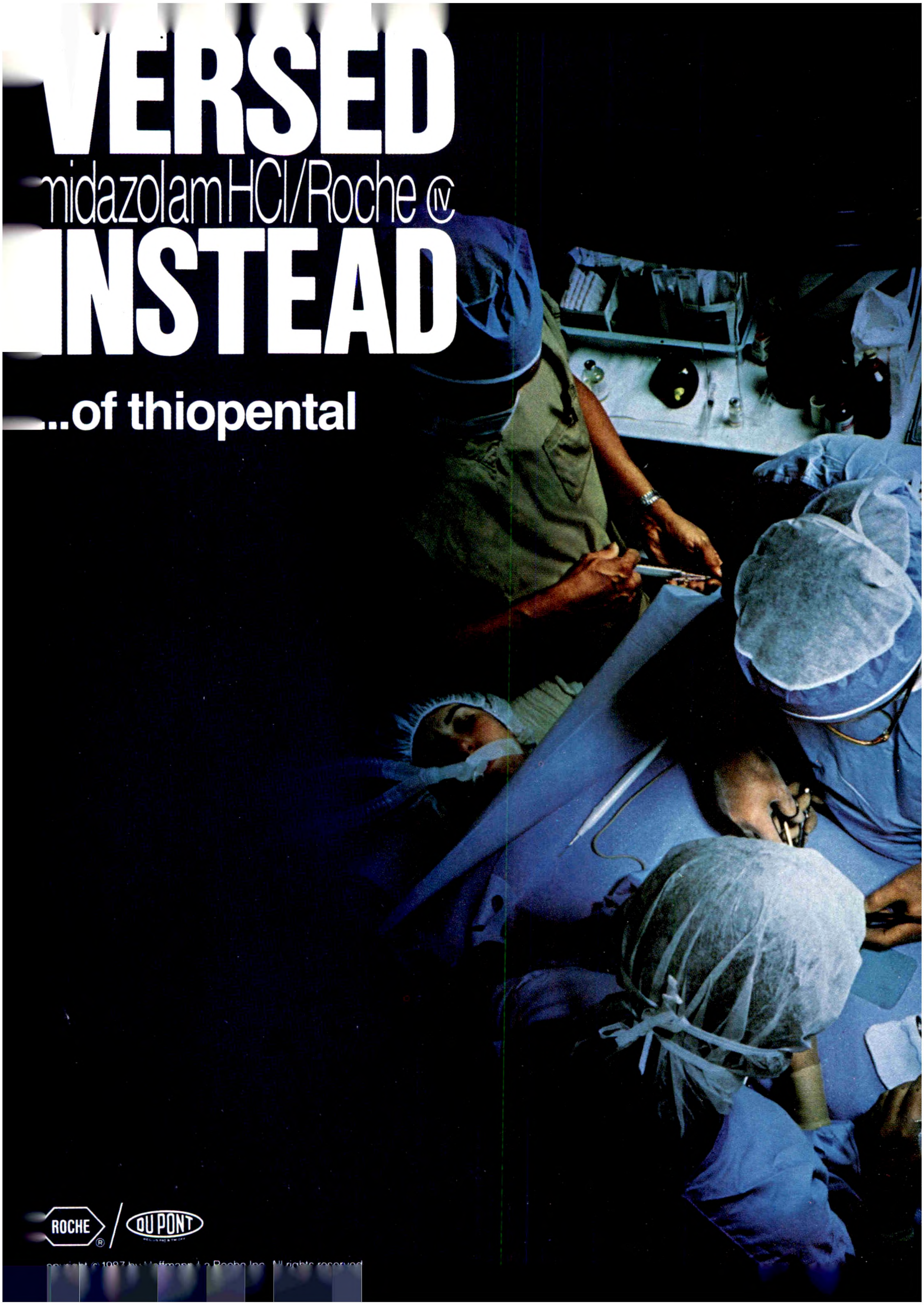
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INDICATIONS: IM: preoperative sedation; to impair memory of perioperative events. **IV:** conscious sedation prior to short diagnostic or endoscopic procedures, alone or with a narcotic; induction of general anesthesia before administration of other anesthetic agents; as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia) for short surgical procedures (longer procedures have not been studied). When used IV, VERSED is associated with a high incidence of partial or complete impairment of recall for the next several hours.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen and resuscitative equipment for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression; should be administered as induction agent only by a person trained in general anesthesia. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred, predominantly in older chronically ill patients and/or with concomitant use of other cardiorespiratory depressant agents. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs.

Guard against unintended intra-arterial injection; hazards in humans unknown Avoid extravasation.

Higher risk surgical or debilitated patients require lower dosages for induction of anesthesia, premedicated or not.

Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure have a 1.5- to 2-fold increase in elimination half-life, total body clearance and volume of distribution of midazolam. Patients with congestive heart failure have a 2- to 3-fold increase in the elimination half-life and volume of distribution of midazolam. Patients over 55 require lower dosages for induction of anesthesia, premedicated or not. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: *General:* Increased cough reflex and laryngospasm may occur with peroral endoscopic procedures. Use topical anesthetic and make necessary countermeasures available; use narcotic premedication for bronchoscopy. Decrease intravenous doses by about 30% for elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or circulatory effects noted following administration of succinylcholine.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant. 3. Inform your physician if you are nursing.

Drug interactions: The hypnotic effect of intravenous VERSED is accentuated by premedication, particularly narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage of VERSED according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of intramuscular VERSED for premedication.

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No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions. Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: The use of injectable VERSED in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness of VERSED in children below the age of 18 have not been established.

ADVERSE REACTIONS: Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. Serious cardiorespiratory adverse events have also occurred. (See WARNINGS.)

In the conscious sedation studies, hypotension occurred more frequently after IV administration in patients concurrently premedicated with meperidine. During clinical investigations, three cases (0.2%) of transient fall in blood pressure greater than 50% were reported during the induction phase.

Reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity and combativeness have been reported. (See DOSAGE AND ADMINISTRATION.)

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special Sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. *Miscellaneous.* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

DOSAGE AND ADMINISTRATION: Individualize dosage. Elderly and debilitated patients generally require lower doses. Adjust dose of IV VERSED according to type and amount of premedication. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest, especially in elderly or debilitated patients. (See WARNINGS.) *IM use:* Inject deep in large muscle mass. *IV use:* Administer initial dose over 20 to 30 seconds for induction of general anesthesia. For conscious sedation administer initial dose over 2 to 3 minutes. May be mixed in the same syringe with morphine sulfate, meperidine, atropine sulfate or scopolamine. Compatible with 5% dextrose in water, 0.9% sodium chloride and lactated Ringer's solution.

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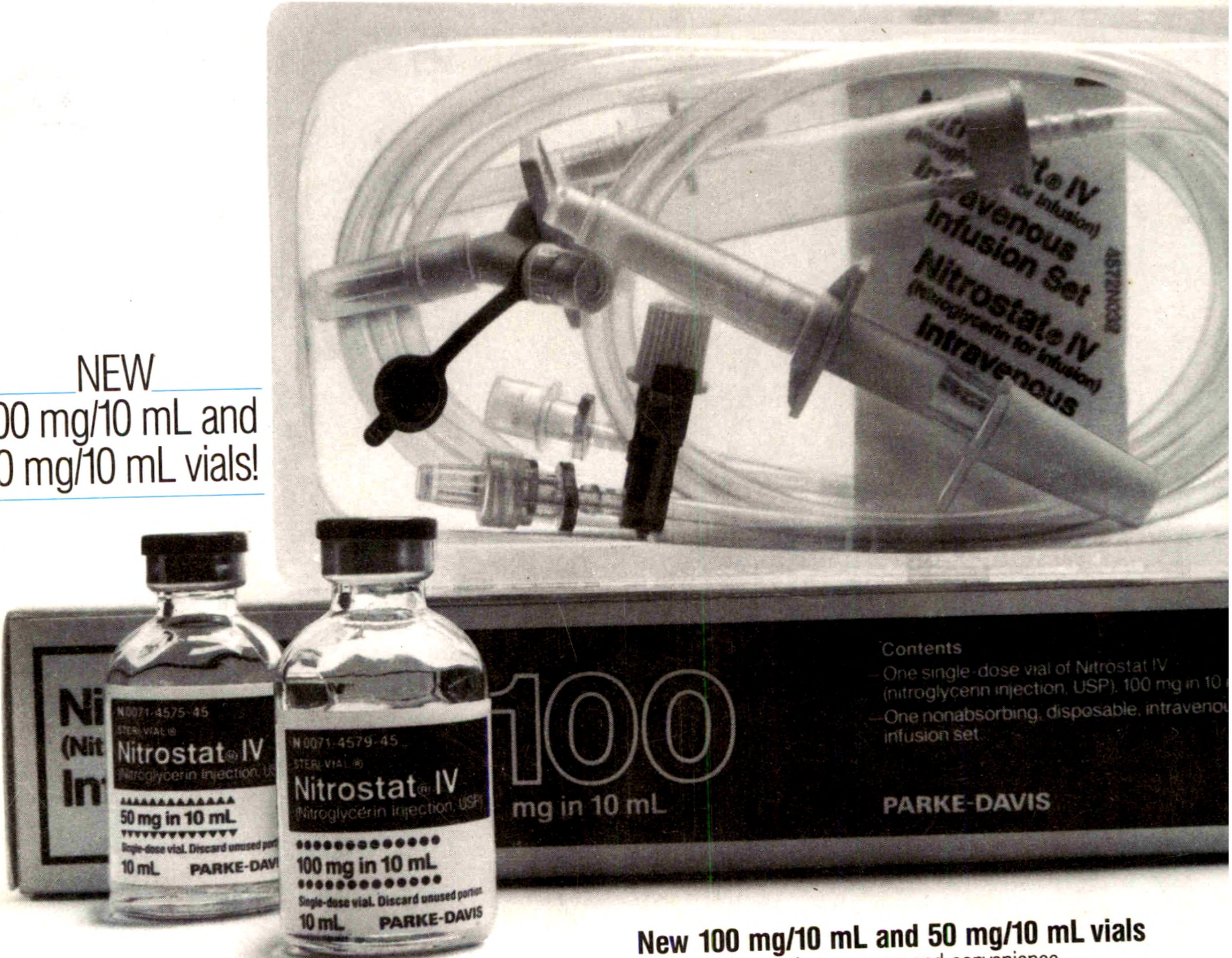

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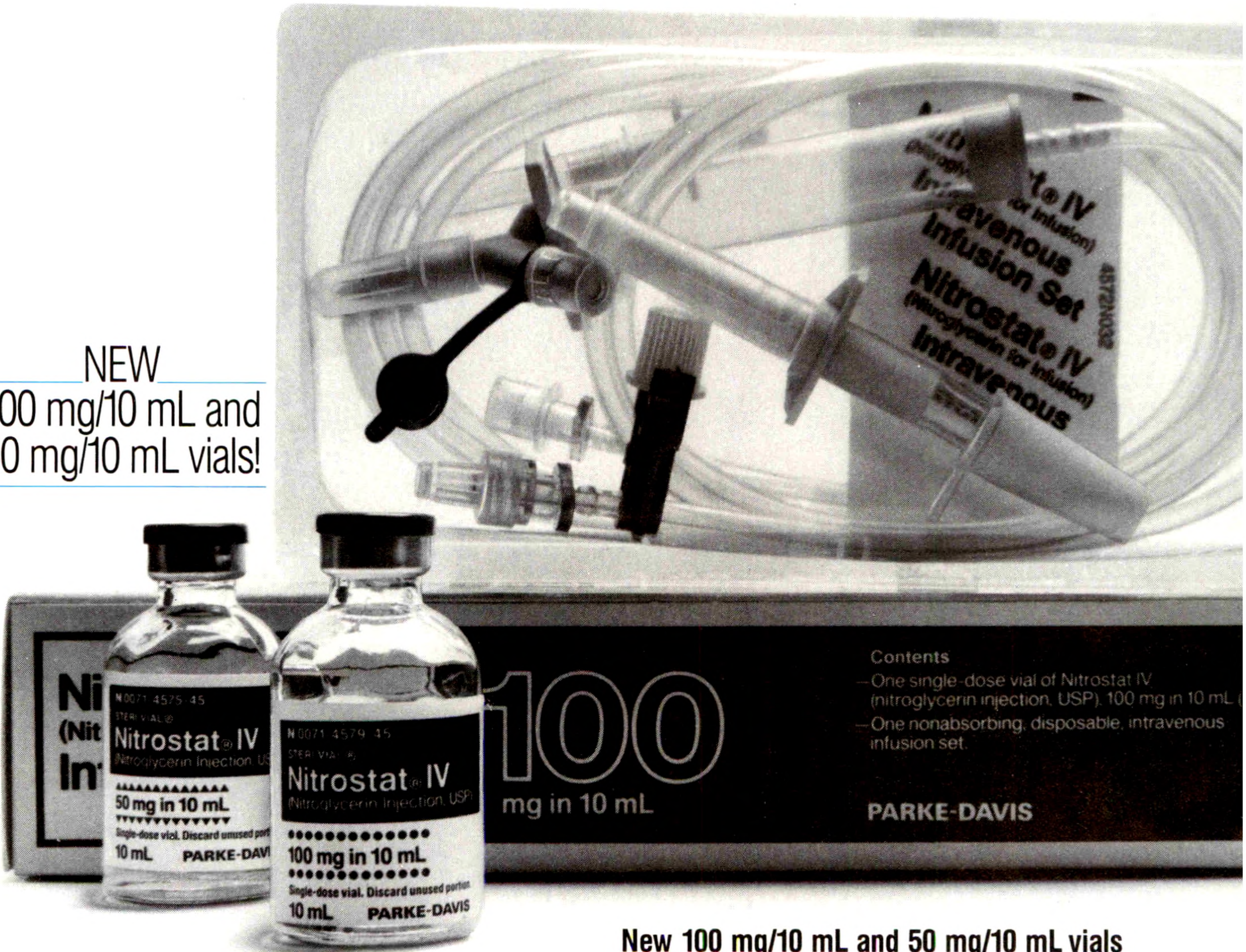

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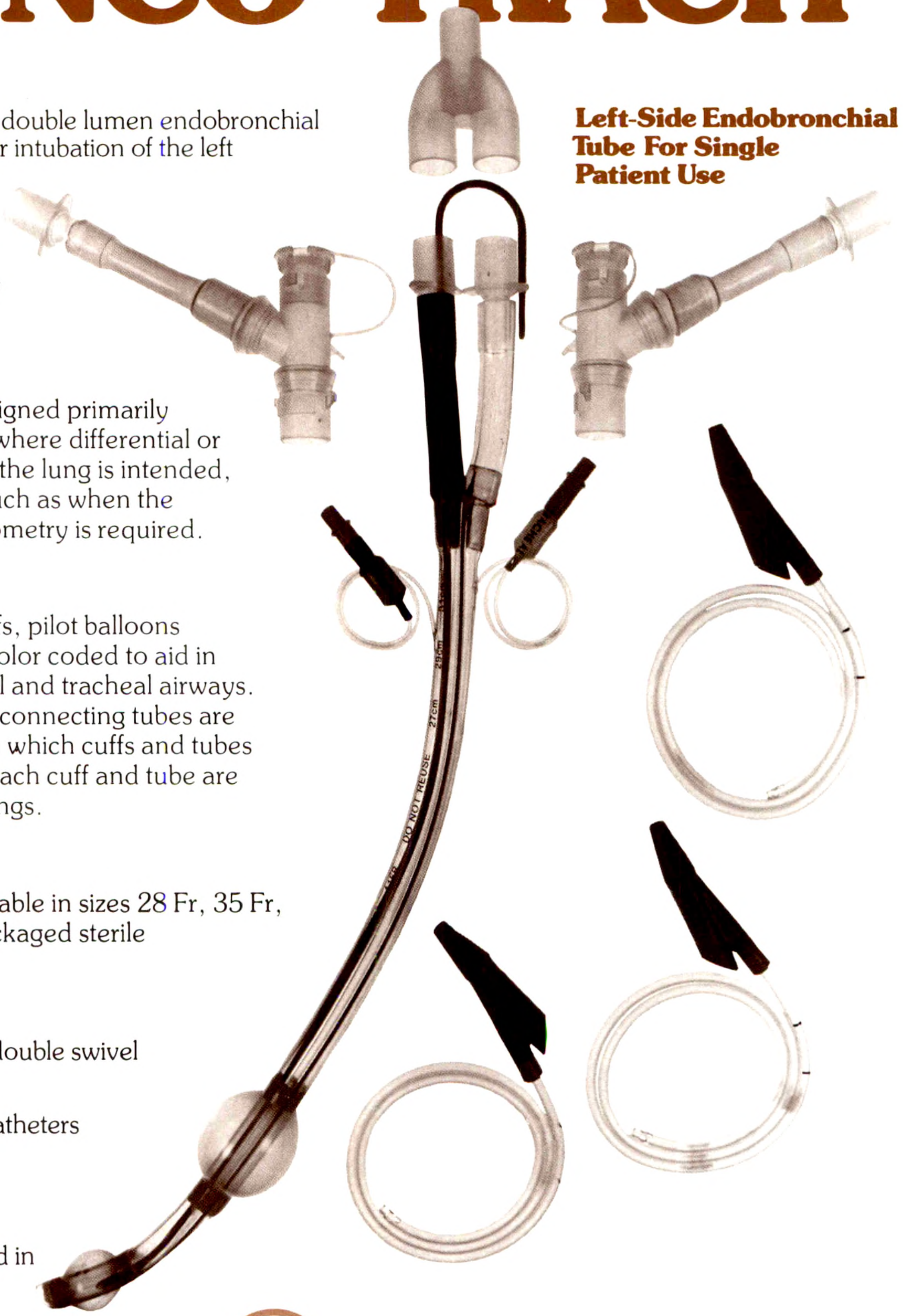

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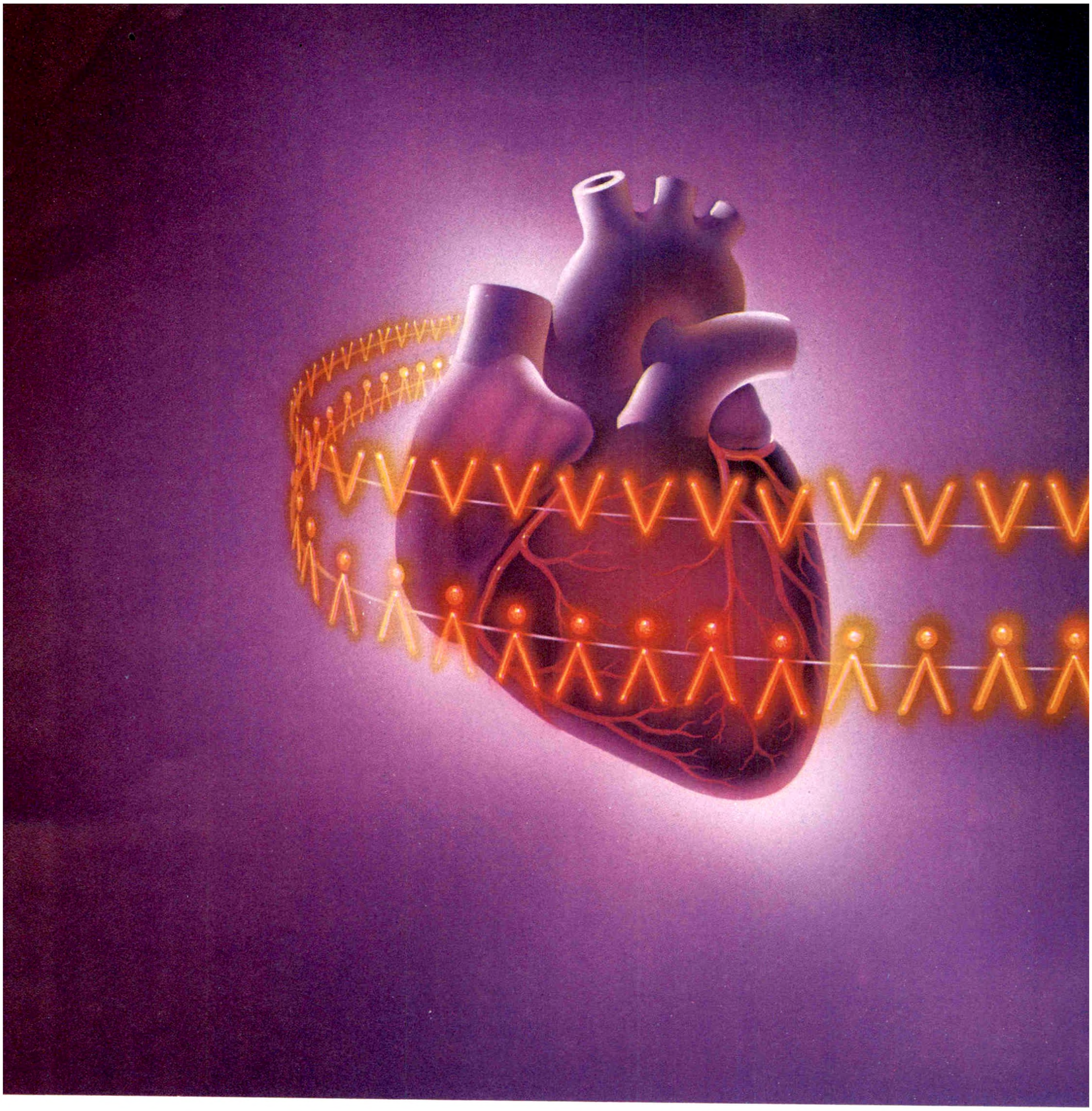

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of SUFENTA.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

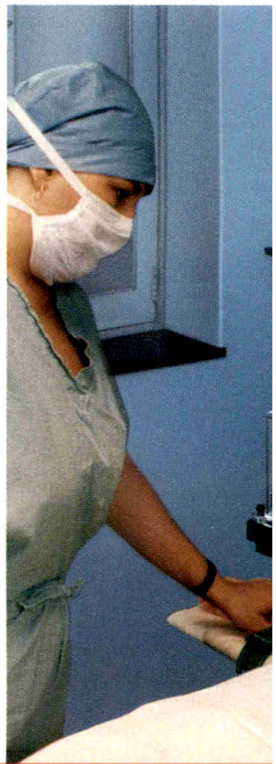
DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

JANSSEN PHARMACEUTICA

Janssen Pharmaceutica Inc.
Piscataway, NJ 08854

U.S Patent No. 3,998,834
7618504-M
January 1986, March 1986
JPI-710

For outpatient anesthesia



Rapid

Well-suited to the rapid turnover of outpatient cases, the low solubility of isoflurane in blood and tissue (only that of nitrous oxide is lower) enables you to quickly adjust the level of anesthesia to patient and surgical requirements.

Following anesthesia, a rapid washout and prompt recovery provide for your early patient assessment. Patient alertness and cooperation can facilitate handling in the outpatient setting.

Complete

Without *any* other agent or premedicant, isoflurane provides *every* action required for a complete anesthetic, on a closely controlled, breath-by-breath basis: unconsciousness, surgical analgesia, amnesia, and good surgical muscle relaxation—a useful advantage for laparoscopies and orthopedic work, and one that begins when the anesthetic begins and *ends* with elimination of the anesthetic, thereby decreasing the risk of residual paralysis in the PAR.

Because isoflurane is a complete anesthetic when given alone in oxygen or room air, *nitrous oxide can be eliminated* if you choose. Isoflurane anesthetics are seldom complicated and prolonged by postoperative nausea and vomiting.

FORANE® (isoflurane, USP)

Excellent Safety Profile

Stability of heart rhythm and good cardiac output are notable features of an isoflurane anesthetic. CNS excitation does not occur at any concentration or $PaCO_2$ level. Virtually 100% of isoflurane is exhaled unchanged from the patient (only 0.17% of the isoflurane taken up is recovered as metabolites). This near absence of metabolic by-products all but assures an absence of hepatic or renal toxicity from metabolism.

Anaquest

BOC Health Care

For outpatient anesthesia

FORANE® (isoflurane, USP)

Rapid...Complete...Excellent Safety Profile

CAUTION: Federal Law Prohibits Dispensing without Prescription.

DESCRIPTION

FORANE (isoflurane, USP) a nonflammable liquid administered by vaporizing, is a general inhalation anesthetic drug. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:

```
      F   H       F
      |   |       |
  F — C — C — O — C — H
      |   |       |
      F   Cl      F
```

Some physical constants are:

Molecular weight		184.5
Boiling point at 760 mm Hg		48.5 °C (uncorr.)
Refractive index n_D^{20}		1.2990-1.3005
Specific gravity 25 °/25 °C		1.496
Vapor pressure in mm Hg**	20 °C	238
	25 °C	295
	30 °C	367
	35 °C	450

**Equation for vapor pressure calculation:

$$\log_{10}P_{vap} = A + \frac{B}{T} \quad \text{where. } A = 8.056,\ B = -1664.58,\ T = °C + 273.16 \text{ (Kelvin)}$$

Partition coefficients at 37 °C	
Water/gas	0.61
Blood/gas	1.43
Oil/gas	90.8
Partition coefficients at 25 °C - rubber and plastic	
Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinyl chloride/gas	110.0
Polyethylene/gas	~2.0
Polyurethane/gas	~1.4
Polyolefin/gas	~1.1
Butyl acetate/gas	~2.5
Purity by gas chromatography	>99.9%
Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec. and 23 °C	None
Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec. and 23 °C	Greater than useful concentration in anesthesia

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave U.V. light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

CLINICAL PHARMACOLOGY

FORANE (isoflurane, USP) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is as follows:

Age	100% Oxygen	70% N_2O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal $PaCO_2$, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 mL of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

Pharmacokinetics: Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

INDICATIONS AND USAGE

FORANE (isoflurane, USP) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Known sensitivity to FORANE (isoflurane, USP) or to other halogenated agents.

Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS

Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

FORANE (isoflurane, USP) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

PRECAUTIONS

General: As with any potent general anesthetic, FORANE (isoflurane, USP) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

Information to Patients: Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N_2O.
See CLINICAL PHARMACOLOGY.

Carcinogenesis: Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have a possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO_2 absorption system (hot canister). PaO_2 and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

ADVERSE REACTIONS

Adverse reactions encountered in the administration of FORANE (isoflurane, USP) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting and ileus have been observed in the postoperative period. As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

OVERDOSAGE

In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION

Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane, USP) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for isoflurane;

b) vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula:

$$\%\ \text{isoflurane} = \frac{100\, P_V F_V}{F_T (P_A - P_V)}$$

where:
P_A = Pressure of atmosphere
P_V = Vapor pressure of isoflurane
F_V = Flow of gas through vaporizer (mL/min)
F_T = Total gas flow (mL/min)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia may be sustained with a 1.0 to 2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5 to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

HOW SUPPLIED

FORANE (isoflurane, USP), NDC 10019-360-40, is packaged in 100 mL amber-colored bottles.

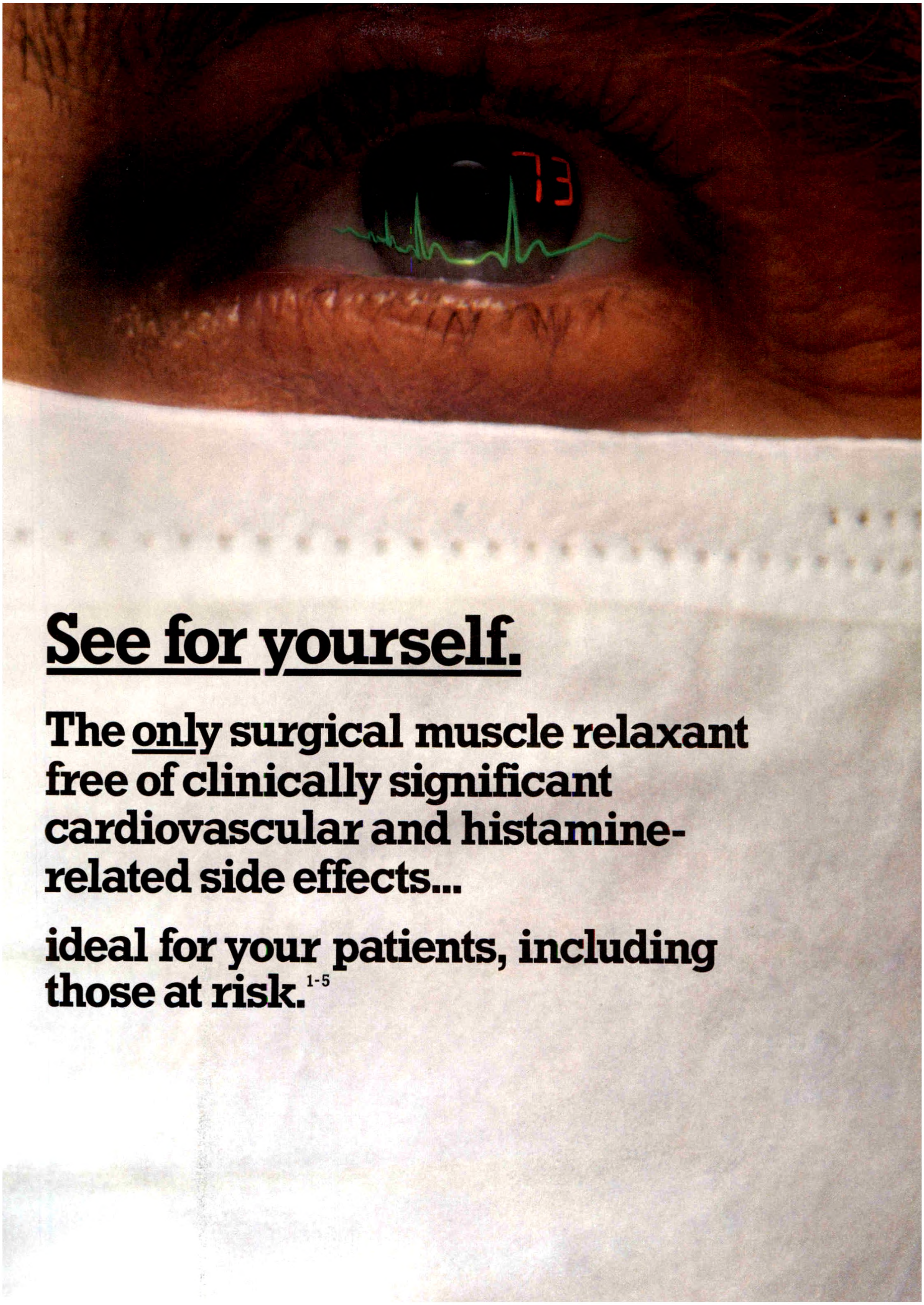
Storage: Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

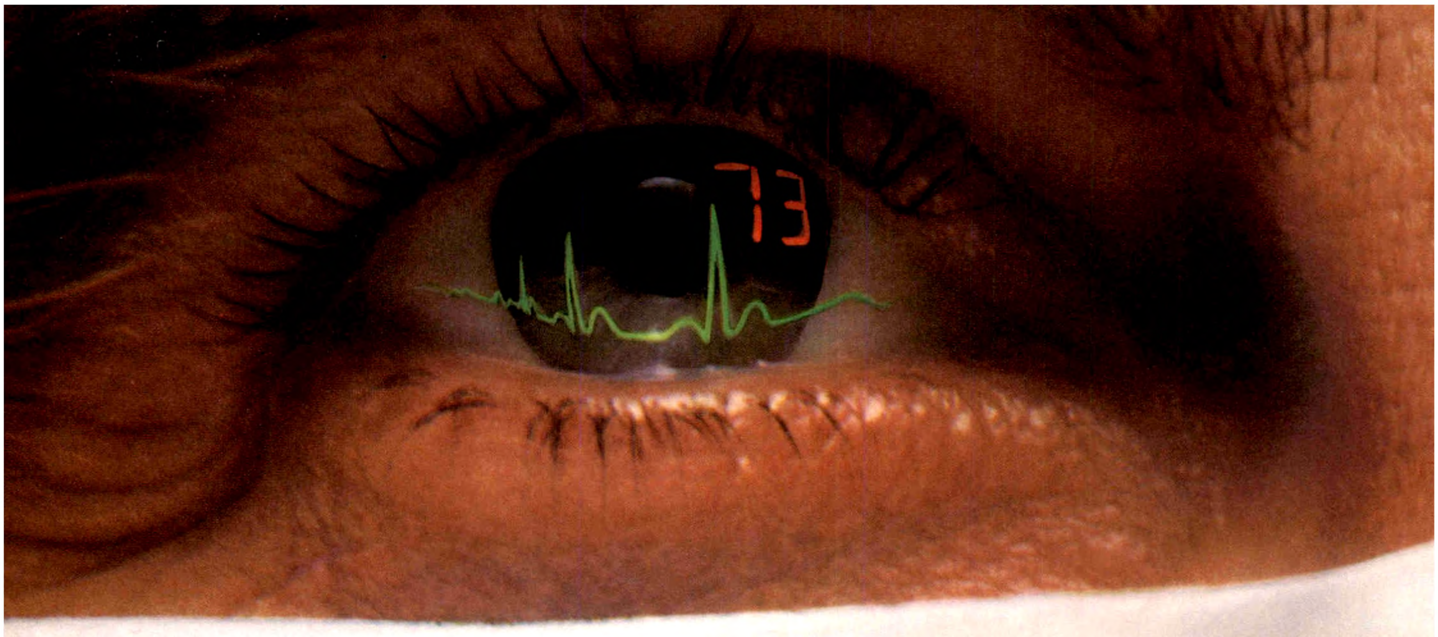
A-0336 Revised 10-85

Anaquest Forane® (isoflurane, USP)

Anaquest
2005 West Beltline Highway
Madison WI 53713 2318
608 273 0019 800 ANA DRUG
A Division of BOC Inc

BOC Health Care

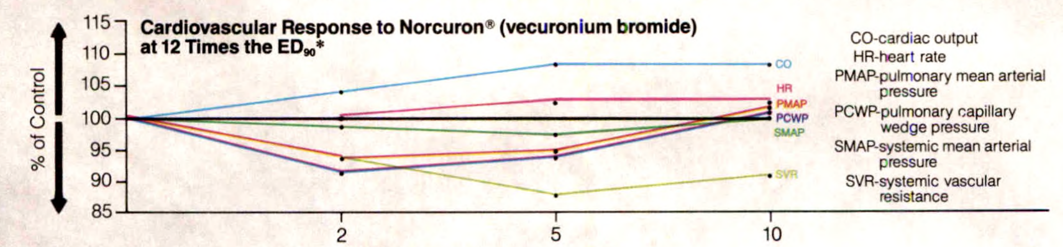

See for yourself.
The only surgical muscle relaxant free of clinically significant cardiovascular and histamine-related side effects...
ideal for your patients, including those at risk.[1-5]



See the safety for yourself.

Free of clinically significant cardiovascular effects.*

NORCURON® is the only surgical muscle relaxant for which no clinically significant cardiovascular effects were observed in clinical trials.[1-4] In fact, even at 12 times effective doses, under halothane anesthesia,[1] NORCURON® produced no tachycardia, hypotension, or abnormalities of cardiodynamic function.



*Adapted from Morris et al.[1]

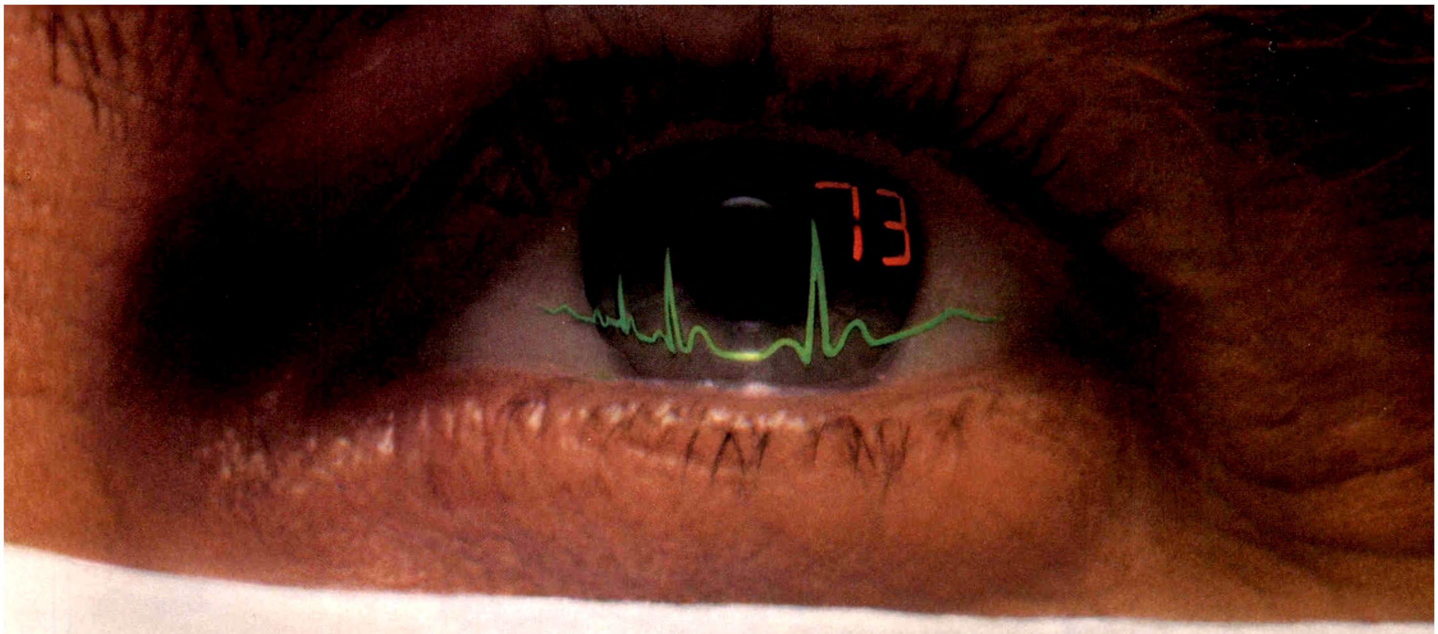
Histamine release or histamine-related side effects unlikely to occur...even at 3.5 times the ED_{95}.[5]

NORCURON® has not been shown to significantly affect circulating histamine, mean arterial blood pressure, and heart rate even in doses at the upper extreme of the recommended clinical range.[5]

The Effect of Nondepolarizing Muscle Relaxants*

Drug	Dose (mg/kg)	xED_{95}	Histamine (Percent of Control)	Mean Arterial Pressure (Percent of Control)	Heart Rate (Percent of Control)
Tubocurarine	0.5	1	410	78	116
Metocurine	0.5†	2	212	79	119
Atracurium	0.6†	3	192	80	108
Vecuronium	0.1	1.7	117	100	99
Vecuronium	0.2	3.5	87	99	102

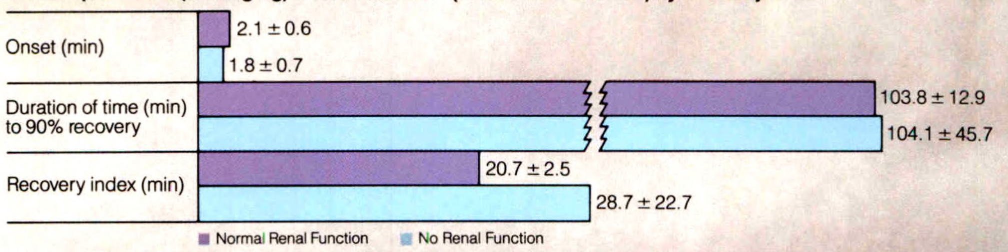
*Adapted from Basta et al.[5]
†0.1 mg/kg higher than recommended dose.



Performance unaffected by renal function.[6]

Despite administration of high doses of NORCURON®, no significant differences in onset time, duration of action, or recovery index have been noted between patients with and without renal function.[6]

Comparative Indices of Neuromuscular Blockade for Patients With and Without Renal Function Given Equal Doses (0.14 mg/kg)* of NORCURON® (vecuronium bromide) by Bolus Injection†



*Although high doses of NORCURON® were used to assess its pharmacokinetics, it is recommended that the initial dose not exceed 0.08 to 0.1 mg/kg.

†Adapted from Miller et al.[6]

The surgical muscle relaxant ideal for virtually all patients including those at risk.

Norcuron®

(vecuronium bromide) injection

See full prescribing information on following page.

References: 1. Morris RB, et al: The cardiovascular effects of vecuronium (ORG NC 45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1983; 58:438-440. **2.** Durant NN: Norcuron®—a new nondepolarizing neuromuscular blocking agent. *Semin Anesth* 1982; 1:47-56. **3.** Krieg N, Crul JF, Booij LH: Relative potency of ORG NC 45, pancuronium, alcuronium, and tubocurarine in anesthetized man. *Br J Anaesth* 1980; 52:783-787. **4.** Gallo JA, et al: Hemodynamic effects of bolus injection of vecuronium in cardiac surgical patients. *Anesthesiology* 1984; 61:A63. **5.** Basta SJ, et al: Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiology* 1983; 59:A273. **6.** Miller RD, et al: Pharmacokinetics of vecuronium in patients with kidney disease, in Agoston S, et al (eds): *Clinical Experiences with Norcuron (ORG NC 45, Vecuronium Bromide).* Amsterdam, Excerpta Medica, 1983, p 124.

Norcuron® (vecuronium bromide) injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: NORCURON® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2β, 3α, 5α, 16β, 17β)-3, 17-bis(acetyloxy)-2-(1-piperidinyl)androstan-16-yl]-1-methyl-, bromide.

Norcuron® is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

CLINICAL PHARMACOLOGY: Norcuron® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about 1/3 more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron® doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED_{90} (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® may be decreased by approximately 15% (see DOSAGE AND ADMINISTRATION section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect on the duration o neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the neuromuscular block produced by Norcuron® is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron® induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

Pharmacokinetics: At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron® varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron® (vecuronium bromide) injection has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

NO REFRIGERATION REQUIRED

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron®; equipotent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron®. Limited data derived from patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary capillary wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease). Limited clinical experience (3 patients) with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

INDICATIONS AND USAGE: Norcuron® is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: None known.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: Renal Failure: Norcuron® is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTANT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

Norcuron® has no known effect on consciousness, the pain theshold or cerebration. Administration must be accompanied by adequate anesthesia.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY). The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®; therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron® during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

OVERDOSAGE: There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION: Norcuron® (vecuronium bromide) injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution | 5% glucose in saline
5% glucose in water | Lactated Ringer's

HOW SUPPLIED: 5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile water for injection as the diluent. Boxes of 10 (NDC#0052-0442-17).

5 ml vials (contains 10 mg of active ingredient) only. DILUENT (Sterile Water for Injection, USP) NOT SUPPLIED. Boxes of 10 (NDC#0052-0442-57).

STORAGE: PROTECT FROM LIGHT. Store at 15°-30°C (59°-86°F).

AFTER RECONSTITUTION: Solution may be stored in refrigerator or kept at room temperature not to exceed 30°C (86°F). DISCARD SOLUTION AFTER 24 HOURS. DISCARD UNUSED PORTION. SINGLE USE VIALS.

Manufactured for ORGANON INC. by BEN VENUE LABORATORIES, INC., Bedford, OH 44146 ISSUED 5/86

ORGANON INC.
WEST ORANGE, NEW JERSEY 07052

ORG-8025

References: 1. Data on file (Doc. #069-001, 004, 005, 007), Roche Laboratories. **2.** VERSED® (brand of midazolam HCl/Roche) ©, Scientific Summary, Roche Laboratories, Division of Hoffmann-La Roche Inc., Nutley, NJ, 1986.

VERSED®
(brand of midazolam HCl/Roche) ©
INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS: IM: preoperative sedation; to impair memory of perioperative events. **IV:** conscious sedation prior to short diagnostic or endoscopic procedures, alone or with a narcotic; induction of general anesthesia before administration of other anesthetic agents; as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia) for short surgical procedures (longer procedures have not been studied). When used IV, VERSED is associated with a high incidence of partial or complete impairment of recall for the next several hours.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen and resuscitative equipment for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression; should be administered as induction agent only by a person trained in general anesthesia. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred, predominantly in older chronically ill patients and/or with concomitant use of other cardiorespiratory depressant agents. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs.

Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Higher risk surgical or debilitated patients require lower dosages for induction of anesthesia, premedicated or not.

Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure have a 1.5- to 2-fold increase in elimination half-life, total body clearance and volume of distribution of midazolam. Patients with congestive heart failure have a 2- to 3-fold increase in the elimination half-life and volume of distribution of midazolam. Patients over 55 require lower dosages for induction of anesthesia, premedicated or not. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: *General:* Increased cough reflex and laryngospasm may occur with peroral endoscopic procedures. Use topical anesthetic and make necessary countermeasures available; use narcotic premedication for bronchoscopy. Decrease intravenous doses by about 30% for elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or circulatory effects noted following administration of succinylcholine.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant. 3. Inform your physician if you are nursing.

Drug interactions: The hypnotic effect of intravenous VERSED is accentuated by premedication, particularly narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage of VERSED according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of intramuscular VERSED for premedication.

VERSED® (brand of midazolam HCl/Roche)

The use of VERSED as an induction agent may result in a reduction of the inhalation anesthetic requirement during maintenance of anesthesia.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: The use of injectable VERSED in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness of VERSED in children below the age of 18 have not been established.

ADVERSE REACTIONS: Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. Serious cardiorespiratory adverse events have also occurred. (See WARNINGS.)

In the conscious sedation studies, hypotension occurred more frequently after IV administration in patients concurrently premedicated with meperidine. During clinical investigations, three cases (0.2%) of transient fall in blood pressure greater than 50% were reported during the induction phase.

Reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity and combativeness have been reported. (See DOSAGE AND ADMINISTRATION.)

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special Sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. *Miscellaneous:* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

DOSAGE AND ADMINISTRATION: Individualize dosage. Elderly and debilitated patients generally require lower doses. Adjust dose of IV VERSED according to type and amount of premedication. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest, especially in elderly or debilitated patients. (See WARNINGS.) *IM use:* Inject deep in large muscle mass. *IV use:* Administer initial dose over 20 to 30 seconds for induction of general anesthesia. For conscious sedation administer initial dose over 2 to 3 minutes. May be mixed in the same syringe with morphine sulfate, meperidine, atropine sulfate or scopolamine. Compatible with 5% dextrose in water, 0.9% sodium chloride and lactated Ringer's solution.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (*e.g.*, sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

ROCHE LABORATORIES
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Nutley, New Jersey 07110

P.I. 0387

Anesthesia Foundation Book Award

The Anesthesia Foundation announces the fifth award of five thousand dollars for a book judged to be the best written in the field of anesthesiology and submitted before September 15, 1988. The award will be given only to an anesthesiologist working and living in North America.

The award will be given only for a first edition. A book may not have more than two authors, and the senior author must be an anesthesiologist. Books that are part of a series, where each chapter has a different author, will not be eligible. Symposia and reports of meetings are also ineligible. Textbooks will be considered if there are not more than two authors.

The award will be based on timeliness, timelessness, originality, teaching value, sophistication, literary style, illustrations, scientific excellence, succinctness, impact, permanent value, format, and references.

If, in the opinion of the judges, no book merits the award, no award will be made.

Books may be submitted by the author or the book publisher. Books must be received no later than September 15, 1988. Books may have a copyright date of 1987 or 1988, but if they are received after September 15, 1988, they will be considered for the following award, provided a sixth book award is offered.

One copy should be sent to each of the three judges:

Nicholas M. Greene, MD, Professor
Department of Anesthesiology
Yale University School of Medicine
333 Cedar Street
New Haven, Connecticut 06510

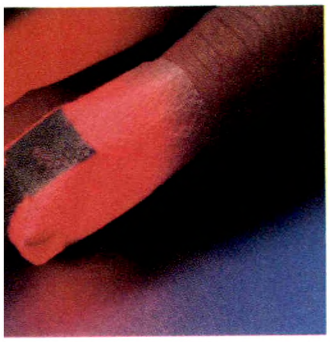
Joseph F. Artusio Jr, MD
Secretary, The Anesthesia Foundation
525 East 68th Street
New York, New York 10021
Attention: Department of Anesthesiology

Leroy D. Vandam, MD
Department of Anesthesia
Brigham and Women's Hospital
75 Francis Street
Boston, Massachusetts 02115

How the ACCUSAT helps solve often associated

roblem 1: ***Patient motion frequently interrupts monitoring.*** Annoying and distracting false alarms often occur. This is especially true for pediatric and neonatal patients. Frequent false alarms can result in confusion and can hinder users from recognizing true alarms.

he ACCUSAT Solution: Sophisticated software rejects noisy pulses and automatically lengthens the



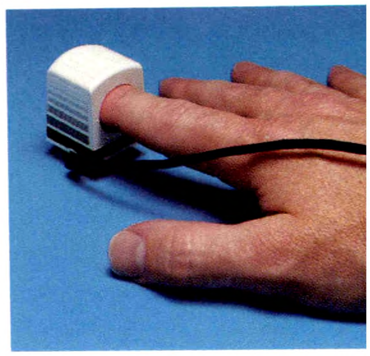
averaging interval to accommodate periods of motion with fewer interruptions. More sophisticated alarms delay sounding for four seconds (while waiting for the signal to return) to reduce the frequency of false alarms. Superior bandage designs hold the sensors more securely in place. And, finally, high output LEDs in the sensors provide a stronger, better quality signal as well as access to more monitoring sites less prone to motion.

'roblem 2: ***Inability to monitor patients with weak pulse levels.*** Poor peripheral circulation, whether from inadequate cardiac output, hypothermia, hypovolemia or vasoconstriction, can make oxygen saturation monitoring impossible or at best erratic.

'he ACCUSAT Solution:

Sophisticated software, using advanced signal processing techniques, and high output LEDs, which provide a better quality, more noise free signal, are able to track weaker pulse levels. In addition, access to a wider range of better perfused monitoring sites is possible.

Problem 3:



Ambient light interrupts monitoring and can cause false readings. Ambient light from surgical lights, room lights and infra-red heaters can trigger false alarms and false readings in some oximeters.

The ACCUSAT Solution: The ACCUSAT continuously measures and compensates for ambient light. In addition, the enclosed finger sensor design and partially opaque bandages minimize the effect of ambient light.

Problem 4: ***High cost of disposable sensors.*** In today's cost conscious environment, hospitals need cost effective monitoring solutions. The high cost of single use disposable sensors greatly increases monitoring cost per patient.

The ACCUSAT Solution:

Reusable sensors and low cost disposable bandages significantly reduce monitoring costs.

Anaquest

Enlon®

(edrophonium chloride injection, USP)

A rapid-acting neuromuscular reversal agent

From the developers of Ethrane® (enflurane) and Forane® (isoflurane)

Anaquest
2005 West Beltline Highway
Madison WI 53713 2318
608 273 0019 800 ANA DRUG
A Division of BOC Inc

60-second reversal
of neuromuscular blockade

- **Onset of reversal significantly faster than with neostigmine or pyridostigmine**—60 seconds versus 7 minutes for neostigmine, 12 minutes for pyridostigmine.[1,2]
- **Duration of reversal comparable to that of neostigmine**—66 minutes versus 76 minutes for neostigmine.[1,2*]
- **Significantly fewer muscarinic side effects and lower atropine requirement than with neostigmine**—edrophonium, 0.5 mg/kg, with only 7 μg/kg atropine, produced minimal change in heart rate or mean arterial pressure compared to noticeable changes in both indexes following neostigmine, 0.04 mg/kg, using *twice* the atropine dose (15 μg/kg).[1,2]
- **May be the preferred reversal agent for atracurium and vecuronium** "...compared with neostigmine, edrophonium has a more complete spectrum of atracurium reversal characteristics, and...antagonizes more rapidly residual atracurium-induced neuromuscular blockade."[3]

  "Edrophonium may in fact be the preferred reversal agent for routine use with [vecuronium], having the advantages that restoration of voluntary muscle function is very rapid, and that the relatively small dose of atropine required minimizes the unwanted side-effects of this drug."[4]

***Note:** When duration of action is adjusted for differences in onset of action, the relative durations are 65 minutes for edrophonium and 69 minutes for neostigmine.

1. Cronnelly R, Morris RB, Miller RD: Edrophonium: duration of action and atropine requirement in humans during halothane anesthesia. Anesthesiology 57:261-266, 1982. 2. Miller RD, et al: Comparative times to peak effect and duration of action of neostigmine and pyridostigmine. Anesthesiology 41:27-33, 1974. 3. Jones RM, Pearce AC, Williams JP: Recovery characteristics following antagonism of atracurium with neostigmine or edrophonium. Br J Anaesth 56:453-457, 1984. 4. Baird WLM, Bowman WC, Kerr WJ: Some actions of ORG NC45 and of edrophonium in the anaesthetized cat and in man. Br J Anaesth 54:375-385, 1982.

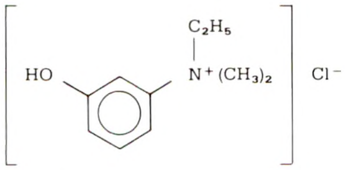
Please see use information on next page.

Anaquest

Enlon® (edrophonium chloride injection, USP)

DESCRIPTION

ENLON (edrophonium chloride injection, USP) is a rapid acting cholinergic (cholinesterase inhibitor). Chemically edrophonium chloride is ethyl (m-hydroxyphenyl) dimethylammonium chloride and its structural formula is:



ENLON contains in each mL of sterile solution.

10 mg edrophonium chloride compounded with 0.45% phenol and 0.2% sodium sulfite as preservative, buffered with sodium citrate and citric acid. Its pH is adjusted to approximately 5.4.

CLINICAL PHARMACOLOGY

ENLON (edrophonium chloride injection, USP) activates neuromuscular transmission primarily by inhibiting or inactivating acetylcholinesterase. By inactivating the acetylcholinesterase enzyme, acetylcholine is not hydrolyzed by acetylcholinesterase and is thereby allowed to accumulate. The accumulation of acetylcholine at the sites of cholinergic transmission facilitates transmission of impulses across the myoneural junction.

INDICATIONS AND USAGE

ENLON (edrophonium chloride injection, USP) is recommended as a reversal agent or antagonist of nondepolarizing muscle relaxants such as tubocurarine, metocurine, atracurium, vecuronium, or pancuronium. It is not effective against depolarizing relaxants such as succinylcholine and decamethonium. It is also useful if used adjunctively in the treatment of respiratory depression caused by curare overdosage.

ENLON is recommended for use in the differential diagnosis of myasthenia gravis. It may also be used as an adjunct to evaluate treatment requirements of the disease, and for evaluating emergency treatment in myasthenic crisis. It is not recommended for maintenance therapy in myasthenia gravis.

CONTRAINDICATIONS

ENLON (edrophonium chloride injection, USP) is not to be used in patients with known hypersensitivity to anticholinesterase agents, or in patients having urinary obstructions of mechanical type.

WARNINGS

It is recommended that 1 mg atropine sulfate should be made available for immediate use, to counteract any severe cholinergic reaction. ENLON (edrophonium chloride injection, USP) should be used with caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Isolated instances of cardiac and respiratory arrest following administration of edrophonium chloride have been reported. It is postulated that these are vagotonic effects.

PRECAUTIONS

General: As with any antagonist of nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance. Should a patient develop "anticholinesterase insensitivity" for brief or prolonged periods, the patient should be carefully monitored and the dosage of anticholinesterase drugs reduced or withheld until the patient again becomes sensitive to them.

Drug Interactions: The drug should not be administered prior to the administration of any nondepolarizing muscle relaxants. The drug should be administered with caution to patients with symptoms of myasthenic weakness who are also on anticholinesterase drugs. Anticholinesterase overdosage (cholinergic crisis) symptoms may mimic underdosage (myasthenic weakness) so the use of this drug may worsen the condition of these patients (see OVERDOSAGE section for treatment).

Pregnancy Category C: It is not known whether ENLON (edrophonium chloride injection, USP) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity, since there have been no adequate and well controlled studies in humans.

Labor and Delivery: The effect of ENLON on the mother and fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary is not known. The effect of the drug on the later growth, development and functional maturation of the child is also unknown.

Nursing Mothers: The safety of ENLON during lactation in humans has not been established.

ADVERSE REACTIONS

A patient in myasthenic crisis, being treated with ENLON (edrophonium chloride injection, USP) should be observed for bradycardia or cardiac standstill and cholinergic reactions if an overdosage is given. Reactions common to anti-cholinesterase agents such as edrophonium chloride are:

Cardiovascular: arrhythmias (especially bradycardia), fall in output leading to hypotension;

Respiratory: increased tracheobronchial secretions, laryngospasm, bronchiolar constriction and respiratory muscle paralysis;

Neurologic: convulsions, dysarthria, dysphonia, and dysphagia;

Gastrointestinal: nausea, vomiting, increased peristalsis, increased gastric and intestinal secretions, diarrhea, abdominal cramps;

Musculoskeletal: weakness and fasciculations;

Miscellaneous: increased urinary frequency, diaphoresis, increased lacrimation, pupillary constriction, diplopia, and conjunctival hyperemia.

OVERDOSAGE

Muscarine-like symptoms (nausea, vomiting, diarrhea, sweating, increased bronchial and salivary secretions and bradycardia) may appear with overdosage (cholinergic crisis) of ENLON (edrophonium chloride injection, USP) but may be managed by the use of atropine. Obstruction of the airway by bronchial secretions can arise and may be managed with suction (especially if tracheostomy has been performed) and by the use of atropine. Signs of atropine overdosage such as dry mouth, flush and tachycardia should be avoided as tenacious secretions and bronchial plugs may form. Should edrophonium chloride overdosage occur:

1. Maintain respiratory exchange.
2. Monitor cardiac function.

Appropriate measures should be taken if convulsions or shock are present.

DOSAGE AND ADMINISTRATION

The recommended adult intravenous injection for antagonism of neuromuscular block:

Administer 1 mL (10 mg) slowly within a period of 30 to 45 seconds, the dosage may be repeated to a maximum total dose of 4 mL (40 mg). Its onset of action is manifest within 30 to 60 seconds after injection. Response should be monitored carefully and assisted ventilation should always be employed. When given to counteract muscle relaxant overdosage, the dose effect on respiration should be observed prior to repeat dosages and assisted ventilation should be employed.

ENLON (edrophonium chloride injection, USP) Test in Differential Diagnosis of Myasthenia Gravis:

Adults:

Intravenous Dosage: Prepare a tuberculin syringe with 1 mL (10 mg) of ENLON and an intravenous needle; intravenously inject 0.2 mL (2 mg) within 15 to 30 seconds. The needle should be left in situ. If a cholinergic reaction (muscarinic side effects, skeletal muscle fasciculations and increased muscle weakness) occurs, discontinue test and intravenously administer 0.4 mg to 0.5 mg atropine sulfate. Inject the remaining 0.8 mL (8 mg) only if no reaction occurs after 45 seconds. The test may be repeated after one-half hour.

Intramuscular Dosage: Intramuscularly inject 1 mL (10 mg) of ENLON. If hyperreactivity (cholinergic reaction) is demonstrated, retest the patient after one-half hour with another intramuscular injection of 0.2 mL (2 mg) ENLON. This will eliminate the possibility of false-negative reactions.

Children:

Intravenous dose in children weighing up to 75 pounds:

Intravenously inject 0.1 mL (1 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 0.5 mL (5 mg). The recommended dose in infants is 0.05 mL (0.5 mg).

Intravenous dose in children weighing above 75 pounds:

Intravenously inject 0.2 mL (2 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 1 mL (10 mg).

Intramuscular Dose: Intramuscularly inject 0.2 mL (2 mg) ENLON in children weighing up to 75 pounds; above this weight, the dose is 0.5 mL (5 mg). All signs of hyperreactivity (cholinergic reaction) noted in the intravenous test will be demonstrated in the intramuscular test; however, there is a two to ten minute delay before reaction.

ENLON (edrophonium chloride injection, USP) Test to Evaluate Treatment Requirements in Myasthenia Gravis:

The test dose of ENLON should follow one hour after oral intake of the drug being used to treat the disease. The recommended dose is 0.1 mL to 0.2 mL (1 mg to 2 mg) administered intravenously. Response to ENLON test dose in treated myasthenic patients is summarized as follows:

Undertreated patient: Myasthenic response; characterized by increased muscle strength (ptosis, diplopia, dysphonia, dysphagia, dysarthria, respiration, limb strength). This indicates inadequate treatment of the myasthenic condition.

Controlled patient: Adequate response; characterized by no change in muscle strength with minimal side reactions (lacrimation, diaphoresis, salivation, abdominal cramps, nausea, vomiting, diarrhea). Fasciculations (orbicularis oculi, facial muscles, limb muscles) may or may not occur. The response indicates that therapy is stabilized.

Overtreated patient: Cholinergic response; characterized by decreased muscle strength and severe side reactions. Fasciculations may be observed. This response occurs in myasthenics who have been overtreated with anticholinesterase drugs.

ENLON (edrophonium chloride injection, USP) Test in Crisis:

Crisis in the myasthenic patient is characterized as a state of severe respiratory distress with inadequate ventilatory exchange, and unpredictable response to medication. If the patient is apneic, achieve ventilatory exchange immediately to avoid cardiac arrest and irreversible central nervous system damage.

The ENLON Test should not be conducted until respiratory exchange is maintained. The cholinergic patient will exhibit further weakness in the muscles of respiration and will have increased oropharyngeal secretions if ENLON is administered. Whereas, upon administration of ENLON the myasthenic patient will demonstrate improved respiration and can be given additional medication. To perform the test prepare a syringe with 0.2 mL (2 mg) ENLON and intravenously inject 0.1 mL (1 mg). The patient's cardiac and respiratory actions should be observed for change. The remaining 0.1 mL (1 mg) may be injected after one minute if no response is noted. If, after the entire 0.2 mL (2 mg) dose has been injected, no improvement in respiration occurs, discontinue all anticholinesterase drugs. Controlled ventilation can be achieved by tracheostomy with assisted respiration.

HOW SUPPLIED

ENLON (edrophonium chloride injection, USP):

NDC 10019-873-15 15 mL multidose vials.

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Effect of Intrathecal Bupivacaine on Somatosensory Evoked Potentials following Dermatomal Stimulation

Claus Lund, MD, Peter Selmar, MD, Ole Bo Hansen, MD, and Henrik Kehlet, MD, PhD

LUND C, SELMAR P, HANSEN OB, KEHLET H. Effect of intrathecal bupivacaine on somatosensory evoked potentials following dermatomal stimulation. Anesth Analg 1987;66:809–13.

The effect of spinal anesthesia with 3.6 ± 0.1 ml (mean ± SEM) of 0.5% bupivacaine on early (<150 msec) somatosensory evoked potentials (SEPs) with electrical stimulation of the L_1 and S_1 dermatomes was examined in 12 patients. The mean level of sensory analgesia (pinprick) was $T_{8,9 \pm 1.0}$ (± SEM) and the mean degree of motor blockade was 1.3 ± 0.1 (Bromage scale). Intrathecal bupivacaine significantly ($P < 0.05$) decreased the amplitude of all SEP components after stimulation of the L_1 dermatome and most components during stimulation of the S_1 dermatome. Intrathecal bupivacaine also increased the latency of SEPs ($P < 0.05$) of both dermatomes. The L_1 SEP disappeared in 7 and the S_1 SEPs in 5 of the 12 patients during neural blockade. In three patients the SEPs disappeared at both locations. Sensory thresholds increased significantly during blockade. We found no correlation between decrease of amplitude and degree of motor blockade or level of sensory analgesia. Thus, intrathecal plain bupivacaine has a strong depressant effect on the neural afferent transmission as assessed by SEPs. However, despite clinically effective blockade as assessed by pinprick and motor blockade nerve potentials after nociceptive stimulation within the area of sensory block were often able to pass to the cerebral cortex.

Key words: ANESTHETIC TECHNIQUES—spinal. BRAIN—somatosensory evoked responses.

The effect of local anesthesia on cortical somatosensory evoked potentials (SEPs) after peripheral electrical stimulation has been examined in several studies (1–4). Infiltration with local anesthetics (1–3) and epidural analgesia (3), for example, decrease amplitude and increase latency of the early components of SEPs. However, components of SEP do not disappear completely during lumbar epidural bupivacaine blockade despite sensory analgesia as assessed by pinprick (4).

The aim of the present study was to determine the effects of intrathecal bupivacaine on neural transmission assessed by SEP after electric dermatomal stimulation.

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Methods

Patients

Twelve patients, all men, mean age 43 years (range 21 to 64) were studied. All were admitted to the hospital for elective herniorrhaphy and none had symptoms, signs or a history of neuromuscular disease. Informed consent was obtained from all patients and the declaration of Helsinki was respected.

Spinal anesthesia

Lumbar puncture (L2–3) was performed with the patient in a lateral horizontal position using a 25-gauge spinal needle and a midline approach. The volume of 0.5% bupivacaine injected was determined by the age of the patients, who were divided into three groups: those 20–45 yr (six patients) received 4.0 ml, those 46–50 yr (three patients) received 3.5 ml and those 51–64 years (three patients) received 3.0 ml. This gradation was performed because several studies have indicated an increase in susceptibility to local anesthetics with increasing age (5–7). On average, the patients received 3,6 ± 0.1 (±SEM) plain bupivacaine, 0.5%, each patient being turned onto the supine hor-

Table 1. Effects of Intrathecal Bupivacaine (0.5%) on Amplitude of Components of the Early Somatosensory Evoked Cortical Potentials after Stimulation of the L_1 and S_1 Dermatomes

	SEP Amplitude (μV)*					
	L_1			S_1		
	Before	During	P	Before	During	P
P_1	0.7 ± 0.1	0.3 ± 0.1	<0.001	1.2 ± 0.2	0.7 ± 0.2	<0.05
N_1	0.9 ± 0.1	0.3 ± 0.1	<0.5	2.0 ± 0.5	1.0 ± 0.3	<0.05
P_2	1.0 ± 0.1	0.3 ± 0.1	<0.02	1.6 ± 0.4	1.0 ± 0.4	<0.05
N_2	1.2 ± 0.2	0.5 ± 0.2	<0.02	1.4 ± 0.3	1.1 ± 0.4	NS
P_3	1.2 ± 0.2	0.5 ± 0.2	<0.02	1.9 ± 0.4	1.2 ± 0.4	<0.05
N_3	1.0 ± 0.11	0.4 ± 0.2	<0.05	1.7 ± 0.3	0.9 ± 0.3	NS
Peak to peak	2.8 ± 0.3	6.3 ± 1.5	<0.05	7.2 ± 0.2	9.6 ± 0.4	<0.01
Sensory threshold (mA)	2.8 ± 0.3	6.3 ± 1.5	<0.05	7.2 ± 0.2	9.6 ± 0.4	<0.01
Stimulation intensity (mA)	11.2 ± 1.0	11.2 ± 1.0	NS	10.8 ± 0.6	10.8 ± 0.6	NS

*Mean ± SEM values.

izontal position immediately after injection. Somatosensory evoked potentials recordings were performed with the patient in the supine position before lumbar puncture and when maximal spread of sensory analgesia (bilateral pinprick) was achieved (15 ± 2 min, mean ± SEM). Motor blockade was assessed by the Bromage scale (8).

Stimulation

The sural nerve, which mainly innervates the area of the S_1 dermatome, was stimulated posterior to the lateral malleolus of the ankle. The sensory nerves of the L_1 dermatome were stimulated at the anterior superior iliac spine. Electrical stimuli of 0.2 msec duration were applied through a bipolar surface electrode (DANTEC/DISA 13 L 22, Copenhagen, Denmark) at a rate of 1.5/sec. The two unilateral areas were stimulated at an intensity of four times the preblock sensory threshold (TS). TS was defined as the midpoint between the stimulus intensity needed for barely detectable perception of stimulation and for barely detectable loss of perception of stimulation. Stimulation of muscle was avoided. Stimulation before intrathecal injection resulted in tolerable pain.

Recording

The cortical activity was recorded from platinum needle electrodes (DANTEC/DISA 25 C 04) at the midline of the scalp, 2 cm posterior and 5 cm anterior (reference) to the vertex located C_Z of the International 10-20 system for EEG recording. During each stimulation procedure, 1000 responses were averaged. A DANTEC/DISA Neuromatic 2000 neuro-myograph was used for stimulation and recording. The amplifier had a band pass (−3dB) of 0.5–1000 Hz, the analysis time was 500 msec. The latency of the onset (0) and the first three positive (P_1-P_3) and negative (N_1-N_3) peaks were measured, as were the amplitudes.

SEP recordings were performed before and after application of analgesia (see earlier). All recordings were performed before surgery.

Statistics

The statistical significance of changes in SEPs associated with injection of bupivacaine was evaluated by Student's *t*-test for paired data. The relation between the extent of analgesia and changes of SEP amplitude, and extent of analgesia versus the degree of motor blockade were evaluated by the least squares method. Comparison between the degree of motor blockade and the decrease of amplitude was evaluated by the Student's *t*-test for unpaired data. $P < 0.05$ was considered statistically significant.

Results

The mean level of analgesia (assessed by pinprick) was $T_{8,9\ \pm\ 1.0}$ (mean ± SEM) and the degree of motor blockade was 1.3 ± 0.1 (mean ± SEM) according to the Bromage scale.

During spinal anesthesia there was a significant reduction in amplitude of the P_1–P_3 and N_1–N_3 peaks of the L_1 SEP and of the P_1–P_3 and N_1 of the S_1 SEP. Likewise, the peak to peak amplitude decreased significantly at both dermatomal levels (Table 1). Figure 1 shows the mean SEP potentials before and during blockade. After intrathecal injection of bupivacaine,

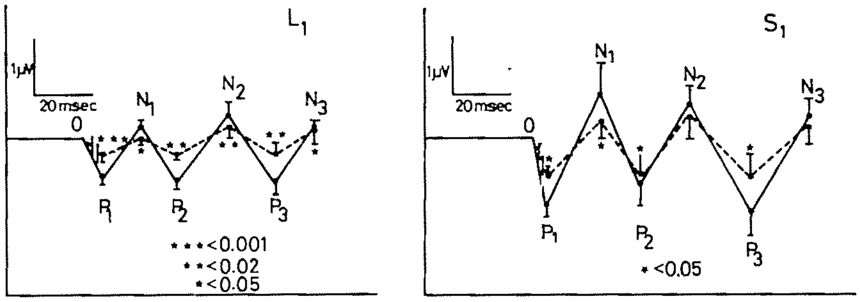

Figure 1. Mean cortical somatosensory evoked potentials before (solid line) and during (dashed line) spinal anesthesia with 0.5% bupivacaine after stimulation of the L_1 and S_1 dermatomes (n = 12; mean ± SEM). The change in latency is not shown in this figure.

Table 2. Effects of Intrathecal Bupivacaine (0.5%) on Latency of the Onset of the First Three Positive-Negative Peaks of the Somatosensory Evoked Cortical Potentials

	SEP Latency (msec)*			
	L_1		S_1	
	Before	During P	Before	During P
Onset	27.0 ± 2.1	<0.01	37.9 ± 3.4	<0.01
P_1	33.6 ± 1.9	<0.01	42.8 ± 5.7	<0.01
N_1	47.2 ± 1.5	<0.05	61.5 ± 4.0	<0.01
P_2	60.3 ± 2.0	<0.05	75.8 ± 4.3	<0.01
N_2	78.2 ± 2.3	<0.02	93.2 ± 4.9	<0.05
P_3	94.3 ± 2.1	<0.01	114.7 ± 4.6	NS
N_3	113.4 ± 3.3	<0.01	135.3 ± 5.6	<0.02

Absolute figures (mean ± SEM) for latency values during blockade are not presented in Table 2 because SEPs were eliminated in seven and five patients after stimulation of L_1 and S_1, respectively. The P denotes level of statistical significance between values before and during block.

*Mean ± SEM values.

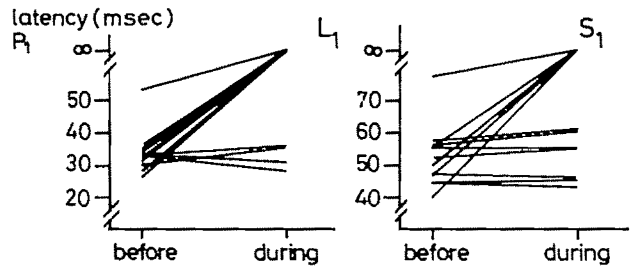

Figure 2. Latency to the first positive peak (P_1) before and during spinal anesthesia with 0.5% bupivacaine after stimulation of the L_1 and S_1 dermatomes. The increase is statistically significant (P < 0.01) at both stimulation sites (n = 12).

the L_1 potentials disappeared in 7 and the S_1 potentials in 5 of the 12 patients. In three patients the SEPs disappeared in both locations.

Latency of the early SEP components increased significantly ($P < 0.05$) after L_1 stimulation. At the S_1 dermatome an increase ($P < 0.05$) in latency was also seen though insignificant in P_3 (Table 2). Absolute figures (mean ± SEM) for latency values during blockade are not presented in Table 2 because SEPs were eliminated in seven and five patients after stimulation of L_1 and S_1, respectively. The P denotes level of statistical significance between values before and during block.

Figure 2 shows the increase of the P_1 latency during blockade ($P < 0.01$ at both stimulation sites). The sensory threshold increased significantly in both stimulation areas during the neural blockade (Table 1).

No correlation was found between the dermatomal level of analgesia and the decrease of the dermatomal evoked potential amplitude ($r < 0.5$; $P > 0.1$), or between the level of analgesia and the degree of motor blockade ($r < 0.5$; $0.1 > P > 0.05$). Reduction of amplitude did not correlate with degree of motor blockade ($P > 0.1$) at either stimulation site (Fig. 3).

Discussion

The present data show that spinal anesthesia produced pronounced reduction of the amplitude and an increase of the latency of the early SEP components within 150 msec. Latency of all SEP components also increased significantly after L_1 and S_1 stimulation, except one peak (P_3), which did not change after stimulation of the S_1 dermatome. Amplitude was significantly reduced in all peaks during blockade, except in N_2 and N_3 after S_1 stimulation. We reported previously (4) that lumbar epidural plain bupivacaine (0.5%) reduced the SEP amplitude after L_1 stimulation, whereas only a minor reduction of the amplitude was seen after stimulation of the S_1 dermatome. In the present study the most pronounced amplitude reduction was seen after L_1 stimulation, probably because of higher concentrations of bupivacaine at this level because of the injection site (L2–3). In contrast to the effect of the epidural block, we found a marked reduction of the S_1 amplitude by intrathecal blockade, an area considered difficult to block during epidural anesthesia (9). The differential effect between spinal and epidural anesthesia on the S_1 segment may be explained by an increased spinal nerve root diameter of the S_1 nerve (9). Furthermore, in contrast to epidural analgesia acting predominantly on the spinal nerve roots and dorsal ganglia, spinal anesthesia may provide a more direct and extensive bathing of the

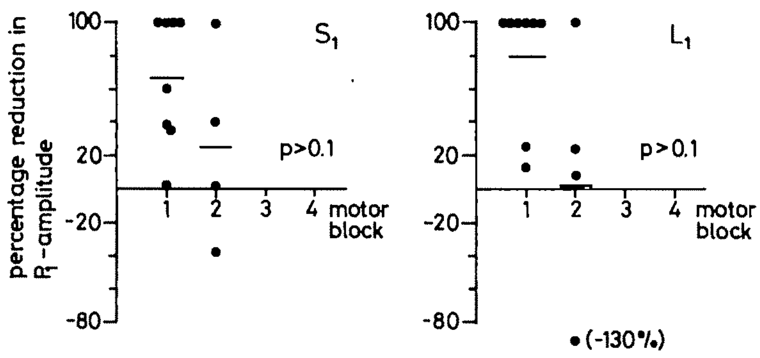

Figure 3. Reductions in P_1 amplitude were not related to degree of motor blockade (Bromage scale) during intrathecal 0.5% bupivacaine after stimulation of the S_1 and L_1 dermatomes (n = 12).

spinal roots in the CSF, and in addition may be more readily taken up in the spinal cord.

Despite sensory analgesia, intrathecal bupivacaine only led to the disappearance of the SEPs in 7 of 12 and 5 of 12 patients after stimulation of L_1 and S_1, respectively, indicating that chemical transection of the spinal cord was not achieved. This finding is in accordance with other clinical studies (10) in which intrathecal bupivacaine 0.5% has been found to provide an inconsistent blockade as assessed by pinprick and touch. Other studies (11,12) have demonstrated a discrepancy in the blocking effect of intrathecal bupivacaine on different fiber types, because the level of sensory analgesia (pinprick) is higher than the sympathetic block as assessed by laser Doppler flowmetry and infrared thermography and skin conductance response, although this has been disputed in recent studies (13). Furthermore, studies have demonstrated (14) that the level of touch discrimination may be several segments lower than level of pinprick after spinal analgesia, and that the level of temperature discrimination may be several segments higher than analgesia to pinprick (15). An explanation for this phenomenon may be a difference in uptake of local anesthetic agents in the different nerve fibers and in spinal cord tissue. Thus, in one study (16) concentrations of local anesthetics varied widely in different neural elements of the spinal cord, thereby possibly explaining the variability in afferent blockade of different nerve tracts during spinal anesthesia.

At the moment it is not possible to relate individual peaks in the SEPs to transmission in special fibers, although it has been suggested that within latencies of 500 msec, the responses come from fast-conducting fibers, (i.e., $A\beta$, $A\delta$) and with latencies of 1.0–2 sec, responses are probably evoked from C-fibers (17).

A correlation between the level of analgesia and the decrease in SEP amplitude or between the spread of analgesia and the degree of motor blockade might thus have been expected. However, this could not be demonstrated, probably because the pinprick and Bromage scale are rough methods in the assessment of neural blockade as compared with SEP.

In conclusion, our study shows that spinal anesthesia with 0.5% bupivacaine has a pronounced inhibitory effect on cortical SEPs after dermatomal electrical stimulation. However, peripherally applied nociceptive stimuli were able in some patients to evoke SEP responses despite the presence of pinprick analgesia. Spinal anesthesia did not invariably result in a complete block of the spinal cord.

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High-Frequency Oscillatory Ventilation in Premature Infants with Respiratory Failure:

A Preliminary Report

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FROESE AB, BUTLER PO, FLETCHER WA, BYFORD LJ. High-frequency oscillatory ventilation in premature infants with respiratory failure: a preliminary report. Anesth Analg 1987;66:814–24.

High-frequency ventilation has been used successfully to manage life-threatening complications in premature infants with lung disease. Here we report a preliminary assessment of the efficacy and safety of high-frequency oscillatory ventilation-(HFO-A, A = active expiratory phase) when used as a primary ventilator in 11 infants of 24–34 weeks gestation who required ventilatory support. HFO-A was initiated after no more than 5.5 hr of conventional mechanical ventilation (CMV). HFO-A at 15 Hz was used for 12–203 hr following a protocol designed for rapid reduction of FI_{O_2} requirements. CO_2 elimination was easily achieved in all infants. Oxygenation was satisfactory, except in one infant with congenital pneumonia. There were four deaths during HFO-A: two pulmonary (one congenital pneumonia; one pulmonary hemorrhage) and two nonpulmonary. The HFO-A protocol utilized lung volume recruitment maneuvers plus mean airway pressures (MAwP) greater than those generally used early in the course of CMV. Therefore, in a subset of infants ≤29 weeks' gestation with respiratory distress syndrome (RDS), ventilator pressures and gas exchange were compared in infants treated with either HFO-A or CMV. Maximum MAwP levels were reached earlier in six infants on HFO-A (5.2 ± 2.5 hr; mean ± SD) than in a comparable group of 9 CMV-treated infants (36 ± 1 hr). This earlier use of high MAwP lowered the FI_{O_2} to <0.4 by 18.9 ± 11 hr with HFO-A as compared with 64 ± 6 hr using CMV, without any evidence of an increase in pulmonary complications. There were 17 complications in the nine CMV-treated infants; and four in the six HFO-A treated ones. We conclude that HFO-A, instituted early and used with a protocol designed for early reduction in FI_{O_2} requirements, demonstrates sufficient efficacy and safety to warrant further clinical trials in the routine management of infant RDS.

Key Words: VENTILATION—high frequency. INTENSIVE CARE—pediatric.

A number of reports now demonstrate that high-frequency ventilation (HFV) can maintain gas exchange in infant respiratory distress syndrome (IRDS) under circumstances in which conventional approaches have been judged inadequate (1–4). In these studies it was believed that the life-threatening severity of complications such as pulmonary interstitial emphysema or bronchopleural fistulae justified trial of this experimental form of ventilation.

To date, however, there are no reports of HFV used as the primary means of ventilation in the management of uncomplicated IRDS. The only reports of HFV in less severe IRDS are those of Marchak et al. (5) and Carlo et al. (6), in which HFV was used for only 1–7 hr throughout the entire course of ventilator therapy. It is possible that, despite the apparent benefit of HFV in the presence of life-threatening complications, it might have an unacceptably high incidence of treatment failure or complications when used in the routine management of IRDS, in circumstances where conventional mechanical ventilation (CMV) generally yields a satisfactory outcome.

The question of HFV safety as a primary means for providing ventilation is of particular concern because both clinical (3) and animal experience to date in both premature baboons (7) and adult models of surfactant deficiency (8,9) has demonstrated that during HFV

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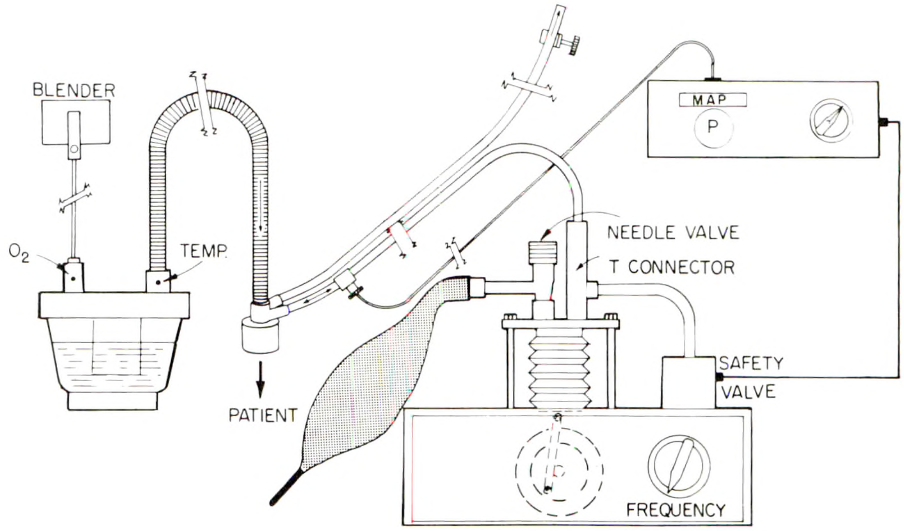

Figure 1. Diagram of the high-frequency ventilator and circuit. See text for details.

some type of periodic large breaths, or a brief (~15 sec) sustained increase in ventilator pressure, is required to achieve effective oxygenation in the atelectasis-prone lung. Such maneuvers are not a necessary part of CMV. They appear necessary, however, during HFV to prevent progressive atelectasis and to achieve the best oxygenation possible for a given operating pressure. Theoretically at least, such volume recruitment maneuvers might cause an unacceptable increase in both acute barotrauma or bronchopulmonary dysplasia (BPD).

Therefore, we carried out a small trial of high-frequency oscillatory ventilation (HFO-A) as a primary mode of ventilatory support in our neonatal intensive care unit. The ventilator used was a high-frequency oscillator that provides active expiratory flow (A = active expiration). Our goal was to determine whether HFO-A has sufficient efficacy and safety to warrant further larger-scale clinical evaluation in the management of routine IRDS.

We followed a protocol that included periodic lung volume recruitment maneuvers that Kolton et al. (8) and Hamilton et al. (9) have shown to be effective in atelectasis-prone animals. Efficacy was assessed by the adequacy of CO_2 elimination ($Pa_{CO_2} < 50$ mm Hg; pH > 7.25) and the ability to lower inspired oxygen requirements below 40%. Safety was evaluated in terms of the incidence of pulmonary complications. Reference values were obtained from infants treated with conventional ventilation in our unit over the same time period, who were of comparable gestational age, weight, and sex.

Methods

Patient Selection

Between February 1983 and June 1984, infants thought to have IRDS were randomly assigned to treatment with CMV or HFO-A following a protocol approved by the hospital's Human Experimentation Review Committee. Informed consent was obtained from the parent(s). None refused participation in the trial. Infants were randomized only if both ventilators were available.

Ideally, randomization and acquisition of informed consent were carried out while infants were still receiving continuous positive airway pressure (CPAP) prior to initiation of ventilator therapy so that therapy could be executed with one ventilator only. However, in seven cases of extreme prematurity and/or birth asphyxia, ventilator therapy was required very shortly after delivery. In these cases, therapy was initiated with CMV and then switched to HFO-A after consent was obtained. Randomization was performed to include the variables of gestational age, birth weight, and sex, using the approach of Taves (10).

Description of Ventilators

HFO-A

The high-frequency ventilator used (HSMVB, Metrex Instruments Ltd., Brampton, Ontario, Canada) is diagrammed in Figure 1. A variable-speed motor drives a shaft that alternately compresses and expands a

small plastic bellows, generating maximal volume displacements of 50 ml over a frequency range of 5–30 Hz with a sinusoidal waveform. Frequency was kept constant at 15 Hz. Stroke volume was adjusted using a needle valve to bleed part of the stroke into a plenum chamber. The actual delivered stroke volumes could not be measured in these infants. However, in rabbits, which have similarly sized lungs, the plethysmographically determined stroke volumes required for eucapnea in normal and surfactant-deficient states range from 2 to 2.5 ml/kg when using identical equipment for HFO-A. All components in continuity with the baby's airway were gas sterilized before use. Oscillations were directed into the patient's endotracheal tube through a 114-cm, ¼-inch inner diameter (id) Tygon tube attached to a Bird infant adapter no. 1229. A second 250-cm, ¼-inch id Tygon tube with a screw clamp at the distal end was attached to the second adapter port so gas could exit from the system. A heated cascade humidifier (Bennett) delivered gas to a port of the Bird adapter. Gross adjustments of mean airway pressure (MAwP) were made by adjusting the screw clamp on the exit tube. Fine adjustments were made by varying the fresh gas flow rate, making sure the flow rate did not fall below 8 L/min so that CO_2 accumulation in the circuit would not occur. Circuit pressure was continuously sampled at a port just proximal to the Bird endotracheal tube adapter using 120 cm of low-compliance tubing connected to a semiconductor transducer (Honeywell 143PC) with a frequency response of 1.0 kHz. The raw pressure signal was processed using a custom-designed device (G. Volgyesi, Biomedical Engineering Department, Hospital for Sick Children, Toronto) that displayed the mean airway pressure digitally and also continuously compared the MAwP with a maximum pressure limit (which can be user selected). If system MAwP exceeded the valve set limit, a solenoid valve automatically opened, decompressing the circuit very rapidly via the T-connector indicated in Figure 1, while activating an audible alarm.

We did extensive in vivo testing of this pressure-monitoring system in surfactant-deficient rabbits to ensure that our MAwP values were, in fact, accurate because of reports that pressures measured at this site seriously underestimate true intrapulmonary pressures (11,12). In such tests, monitoring pressures never differed more than 2 cm H_2O from pressures measured during brief airway occlusions. This level of agreement has been confirmed by Bryan and Slutsky (13) using similar equipment. Only the mean airway pressure can be monitored reliably at this site, because both peak and minimal values are influenced strongly by the physical dimensions of the endotracheal tube at these high frequencies (5).

Table 1. MAwP Selection Protocol

Observation	Action
Tc_{O_2} increases on constant FI_{O_2} after HFO-A initiated even without SI.	Remain at that MAwP. Lower FI_{O_2} appropriately. Attempt decrease in MAwP once $FI_{O_2} < 0.4$. Use SI only if oxygenation deteriorates.
SI improves Tc_{O_2}. Improvement maintained when returned to original MAwP.	Remain at that MAwP. Lower FI_{O_2} appropriately. Repeat SI where indicated.
SI improves Tc_{O_2}. Tc_{O_2} deteriorates over time when returned to original MAwP.	Increase MAwP 2 cm H_2O. Repeat SI. Observe. Repeat sequence until MAwP is found that sustains the improvement in oxygenation gained by the SI.
SI is ineffective. No increase in Tc_{O_2}.	Reevaluate clinical and x-ray picture. Is there a major nonpulmonary shunt?

CMV

The conventional ventilators used (Healthdyne and Sechrist) were both constant-flow, time-cycled, pressure-limited machines.

Selection of Ventilator Settings

HFO-A

We fixed frequency at 15 Hz and varied stroke volume to achieve CO_2 control, as guided by arterial gas tension analysis. The accepted goal for CO_2 elimination with both ventilators was maintenance of $Pa_{CO_2} < 50$ mm Hg with pH > 7.25, unless there was a specific therapeutic indication for hyperventilation. Muscle relaxants were not used during HFO-A. The high-frequency flow pulses were simply superimposed on the patient's spontaneous efforts. Oxygenation was regulated by evaluating FI_{O_2}, the mean airway pressure, and the patient's responsiveness to sustained inflations, by means of the protocol given in Table 1. Initially, when transferring to HFO-A from either CPAP or CMV, we set the HFO-A at the same FI_{O_2} and a MAwP 1–2 cm H_2O higher than the previous system. If a favorable response was seen (i.e., increase in

transcutaneous O_2 tension [Tco_2]), then MAwP was maintained while Fi_{O_2} was lowered progressively. If Tco_2 showed no improvement, a sustained inflation (SI) was given by increasing MAwP 5–10 cm H_2O above the maintenance level for 15–20 sec with the ventilator kept running throughout the maneuver. MAwP was then returned to its previous level. An infant was considered responsive to a sustained inflation if Tco_2 increased acutely by 30 mm Hg or more over the 60–120 sec immediately after MAwP was lowered to its maintenance level. The several possible options and treatment decisions are summarized in Table 1.

Use of SI

Sustained inflations were given after endotracheal tube disconnections, as for repositioning or suctioning, and when the infant demonstrated a decrease in Tco_2 associated with struggling or straining. If the SI was not effective in returning the Tco_2 to its previous level, appropriate Fi_{O_2} adjustments were made.

Weaning

Weaning was performed by reducing Fi_{O_2} as rapidly as possible until <0.4. Mean airway pressure was then reduced in 1 cm H_2O increments every 4–6 hr, unless oxygenation deteriorated. Once the infant required $Fi_{O_2} \leq 0.4$ at a MAwP ≤ 10 cm H_2O, stroke volume was decreased progressively while holding frequency constant at 15 Hz. When stability was achieved with minimal ventilator stroke volume, the infant was connected to CPAP and extubated using the usual clinical criteria. If, despite a low Fi_{O_2} requirement and normal chest x-ray, an infant could not be weaned from HFO-A after 5–8 days because of persistent apnea, the infant was managed using CMV at appropriate low rates and pressures until the apnea resolved.

CMV

Conventional ventilator settings were selected by the attending neonatology staff in consultation with the HFO research team. Peak inspiratory pressures (PIP) were kept <30 cm H_2O whenever possible; inspiratory time was usually less than 50% of the total cycle duration. Increasing Fi_{O_2} requirements were responded to by increasing mean airway pressure by raising positive end-expiratory pressure (PEEP) with or without increases in the percentage of inspiratory time. CO_2 retention was handled by increasing ventilator frequency, adjusting the percentage inspiratory time, and, if necessary, increasing the cyclic pressure swing (i.e., increasing PIP with or without some decrease in PEEP). These rather complex sequences of ventilator adjustments were required because MAwP and tidal volume cannot be independently controlled when using CMV, as they can be when using HFO-A. Mean airway pressure measurements during CMV were made by electronic averaging of the raw pressure signal, the same device being used for all the conventional ventilators. Muscle relaxants were used only if discoordination of patient and ventilator was interfering with effective ventilation. After endotracheal tube suctioning, two or three ventilator breaths were given using the manual control. Weaning was carried out by gradual decreases in Fi_{O_2}, peak and end-expiratory pressures, and ventilator rate, until the infant was on CPAP.

In all infants, continuous Tco_2 monitoring was used to guide ventilator adjustments, in conjunction with arterial gas tension measurements. The research team maintained detailed records of ventilator settings (including MAwP), Tco_2, HR, BP, and arterial Po_2, Pco_2, and pH in both HFO-A- and CMV-treated infants.

General Care

The neonatology staff directed the general care of all infants, so that all infants were cared for using the same protocols for fluid therapy, total parenteral nutrition, and antibiotic therapy. Any respiratory complications such as pneumothorax were dealt with by the attending staff in all cases.

Whenever any study infant died, the pathology department was alerted to take special note of any possible tracheal pathology in the HFO-A group. Lung pathology was evaluated by a single pathologist who was blinded to the clinical course and ventilator type. Results are given as mean ± SEM. Statistical comparisons were performed using Student's unpaired *t*-test, with a *P* value of < 0.05 considered statistically significant.

Results

All HFO-A-Treated Infants

Over the 17-month study period, 11 infants were managed using HFO-A, for a total of 843 hr. Infants ranged from 24 to 34 weeks in gestational age, with birth weights of 680–2950 g. Their clinical characteristics and outcome are summarized in Table 2. Although all were thought to have IRDS at the time of randomization, one turned out to have congenital pneumonia, in one persistent pulmonary hyperten-

Table 2. Clinical Characteristics and Outcome: All HFO-A-Treated Infants

	Gestational age (weeks)	Birth weight (g)	Sex	Hours on CMV prior to HFO-A	Hours on HFO-A	Diagnosis	Pulmonary complications	Cause of death	Comments
Non-survivors									
H-1	24	700	F	4.5	22	RDS	none	intracranial hemorrhage	Died 28 hr Autopsy: no HM mild PIE on left
H-2	24	760	F	4.0	188	PPHN	ptx, day 7	cerebral anoxia	Severe birth asphyxia Hyperventilated to pH 7.55–7.60 at MAwP 9–10 cm H_2O Autopsy: lungs immature; no HM
H-3	<26	880	F	2.0	12	congenital pneumonia	irreversible hypoxia	hypoxia	Autopsy: severe congenital pneumonia, focal mild PIE
H-4	28	1160	M	5.5	34	RDS	pulmonary hemorrhage	pulmonary hemorrhage	Died 39.5 hr Severe birth asphyxia, developed renal failure and bleeding diathesis
Survivors									
H-5	24	880	M	2.75	203	RDS	none	—	Persistent apnea →CMV Days 9–40
H-6	27	680	M	CPAP for 22.5 hr	72	prematurity with apnea	(BPD)	—	→CMV Day 5 for apnea Developed severe BPD while on CMV
H-7	28	1300	M	2.5	87	RDS	bilateral ptx	—	—
H-8	29	1020	F	1.0	24	RDS	none	—	—
H-9	29	1320	M	5.5	103	RDS	none	—	Twin of C-9
H-10	31	1420	M	1.5	65	prematurity with apnea	none	—	Required exchange transfusion for ABO incompatibility
H-11	34	2950	F	2.0	33	RDS	none	—	Infant of diabetic mother Failed CPAP trial

PPHN, persistant pulmonary hypertension of newborn; PIE, pulmonary interstitial emphysema; BPD, bronchopulmonary dysplasia; HM, hyaline membranes; CMV, conventional mechanical ventilation; HFO-A, high frequency oscillatory ventilation with active expiratory phase; CPAP, continuous positive airway pressure; ptx, pneumothorax.

sion was the dominant problem, and in two the oxygenation defect was so minor that a definitive diagnosis of IRDS could not be made. There were four deaths in the HFO-A group of 11 infants, two of which were nonpulmonary in origin (severe cerebral insult). One infant died of congenital pneumonia. Neither HFO-A nor vigorous manual ventilation could achieve adequate oxygenation in this infant preterminally. The fourth infant (H-4), who was severely asphyxiated at birth and required cardiopulmonary resuscitation, died of lethal pulmonary hemorrhage after 34 hr of ventilatory support, at a time when he developed renal failure and a bleeding diathesis. Autopsy examination of lung tissue was performed in the first three cases (Table 2).

There were seven survivors, six of whom had complete radiologic and gas exchange resolution of their primary problem. Infant H-6 had an uneventful course on HFO-A initially, having stable $F_{I_{O_2}}$ requirements of 0.23–0.30 throughout 5 days of HFO-A, but could not be weaned because of apnea. He was given CMV at low pressures (13/5 cm H_2O × 10). By day 11, early signs of BPD became evident on x-ray. By day 15, oxygen requirements reached 70–80% and he required continued ventilation for BPD for 56 days.

Responsiveness to the sustained inflations that were an integral part of the HFO-A protocol was observed in six of the HFO-A-treated infants (Table 3) with individual responses yielding acute T_{CO_2} increases of as much as 230 mm Hg (Fig. 2). In infants H-1, H-8, H-10, and H-11, progressive decreases in oxygen requirements occurred so soon after instituting HFO-A that volume-recruitment maneuvers were not considered necessary. With infant H-3, SIs were not needed

Table 3. Response to Sustained Inflations

	Operating MAwP (cm H_2O)	MAwP during sustained inflation (cm H_2O)	Δ T_{CO_2} (mm Hg)
H-2[a]	10.0	20	38
H-4[a]	9.0	15	40
H-5	20.4	30	43
	13.5	20	52
H-6	15.3–17.0	25	104–230
	15.0–16.0	20	62–128
H-8	15.3–18.1	25	63–66
H-9[a]	10.0–10.3	17.5	35–59

SI, sustained inflation.
ΔT_{CO_2}, maximum T_{CO_2} immediately after the SI minus T_{CO_2} prior to SI.
[a]These SIs were performed to reverse acute decreases in T_{CO_2} that occurred in association with either handling of the infant or spontaneous straining. The other SIs reported represent attempts to improve oxygenation in babies with high oxygen requirements.

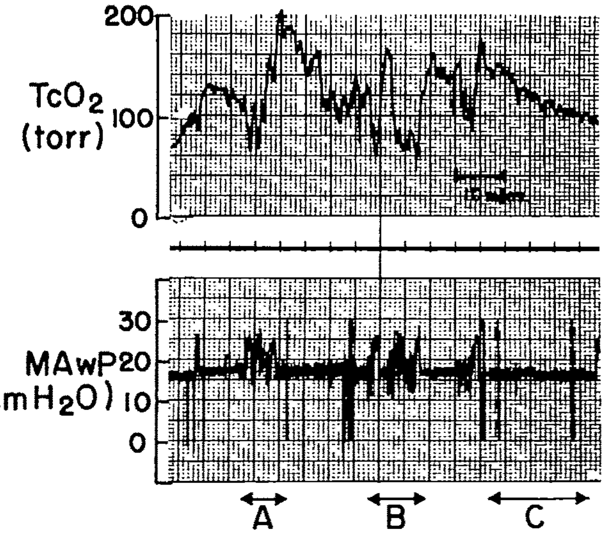

Figure 2. Example of oxygenation response to sustained inflations in infant H-7 during a period of extreme instability at 13 hr of age. T_{CO_2} = transcutaneous oxygen tension. During this period a T_{CO_2} value of 110 mm Hg was equivalent to an arterialized capillary O_2 tension of 50 mm Hg. MAwP = mean airway pressure during HFO-A. During period A, the MAwP was increased to 25 cm H_2O briefly three times over 6 min to reverse abrupt decreases in T_{CO_2} caused by oral suctioning. When the final sustained inflation performed after suctioning was finished, an excessive increase in T_{CO_2}, F_{IO_2} was reduced from 0.70 to 0.58 to return T_{CO_2} to desired levels. During B, three SI maneuvers were used over 10 min, at constant F_{IO_2}, to reverse decreases in T_{CO_2} associated with handling of the infant. Once handling ceased, one further SI was given and then F_{IO_2} was progressively lowered to 0.50 during period C, with all other ventilator settings constant, to return T_{CO_2} to target levels.

initially: preterminally SI attempts to 25 and 30 cmH_2O were ineffective. In general, responsiveness to an SI tapered as the maintenance MAwP requirement decreased, so that infants with MAwP levels of 10–12 cm H_2O rarely demonstrated further need for the volume-recruitment maneuver, being able to recover quickly from transient T_{CO_2} dips spontaneously. Only rarely were SI pressures of >25 cm H_2O utilized. As the maintenance MAwP requirement decreased with recovery of the infant, SI pressures were reduced in parallel fashion. In several infants, periods of hypoxia occurred during which responsiveness to the SI maneuver disappeared. If no pulmonary cause could be detected on chest x-ray, these were considered to be due to extrapulmonary shunting. Further SI maneuvers were not attempted. Instead F_{IO_2} was increased as required until the episode spontaneously terminated.

Comparative Data: Infants ≤ 29 Week with RDS

In Table 4, gas exchange data and pulmonary complications are reported for all infants ≤29 weeks' gestation who had a definite diagnosis of RDS and required ventilator support. Six infants were managed with HFO-A; nine with CMV. Only infants who eventually reached an F_{IO_2} requirement of <0.4 were included in the statistical comparisons. This approach excludes four infants who died at 28 hr of age or less, H-1 of intracranial hemorrhage, and C-1, C-2, and C-3 of refractory hypoxia.

The mean weights of the two groups were not significantly different. All infants exhibited the classic x-ray features of RDS. The early F_{IO_2} requirement was defined as the highest F_{IO_2} required to achieve an arterial P_{O_2} of 60–80 mm Hg over the first 2–6 hr of ventilator therapy. The early F_{IO_2} requirements averaged 0.90 ± 0.06 in the infants subsequently treated with HFO-A; and 0.66 ± 0.05 in the CMV group. Gas exchange was also assessed over this time period by calculating the ratio of measured arterial to calculated alveolar oxygen tension (a/A ratio), assuming a respiratory quotient of 0.8, by the method of Gilbert and Keighley (14). The average a/A ratios over this same period were 0.10 ± 0.01 in HFO-A-treated infants, and 0.23 ± 0.02 in the CMV-treated infants.

Oxygenation improved more rapidly during HFO-A. A sustained F_{IO_2} requirement of <0.4 was reached by 18.9 ± 11 hr of HFO-A, as compared with 64 ± 6 hr with CMV. This fairly rapid reduction of F_{IO_2} requirement reflects the use of higher mean airway pressures early in the course of treatment with HFO-A. Maximal MAwP levels of 17.7 ± 0.9 cm H_2O were reached by 5.2 ± 2.5 hr of treatment during HFO-A. In the CMV-treated infants, the maximal MAwP levels of 15.1 ± 1.5 cm H_2O were reached at 35.8 ± 1.1 hr of therapy.

Although the HFO-A protocol resulted in the early use of higher levels of MAwP plus periodic sustained

Table 4. Infants ≤29 Week with Respiratory Distress Syndrome: Time Course of Gas Exchange and Mean Airway Pressures (MAWP)

	Gestational age (weeks)	Birth weight (g)	Sex	Early FI_{O_2}	Early a/A	Time to FI_{O_2} < 0.4 (hr)	Time to FI_{O_2} < 0.3 (hr)	Time to Max MAwP (hr)	Max MAwP (cm H_2O)	Pulmonary complications	Outcome
HFO-A treated											
H-1[a]	24	700	F	0.60	0.15	never	never	2.0	18.8	—	Died (28 hr)
H-4	28	1160	M	1.0	0.08	16.0	never	4.0	20.0	pulmonary hemorrhage irreversible hypoxia	Died (39.5 hr)
H-5	24	880	M	1.0	0.08	2.25	4.0	0.75	16.0	—	Survived
H-7	28	1300	M	1.0	0.11	62.0	74.0	15.0	17.5	bilateral ptx	Survived
H-8	29	1020	F	0.8	0.09	3.0	12.5	2.5	15.5	—	Survived
H-9[b]	29	1320	M	0.7	0.13	11.0	20.0	3.5	19.4	—	Survived
Mean (± SEM)	27.6 (0.9)	1136 (84)	—	0.9 (.06)	0.10 (.01)	18.9 (11.0)	27.6 (12.9)	5.2 (2.5)	17.7 (.9)	—	—
CMV-treated											
C-1[a]	<26	980	M	<0.8	0.30	never	never	9	21.4	irreversible hypoxia severe PIE (x-ray & autopsy) widespread HM	Died (10 hr)
C-2[a]	<26	640	F	<1.0	0.38	never	never	6	20.4	Lt ptx PIE (x-ray & autopsy) irreversible hypoxia widespread HM	Died (9 hr)
C-3[a]	28	1340	F	0.8	0.11	never	never	13	22	bilateral ptx; severe PIE (x-ray & autopsy) irreversible hypoxia widespread HM & atelectasis	Died (15 hr)
C-4	27	1000	M	0.8	0.28	58	76	36	12	bilateral ptx; PIE PDA ligation; BPD	Survived
C-5	28	1260	M	0.5	0.29	49	73	38	12	—	Survived
C-6	29	920	M	0.54	0.21	54	67	33	21.5	—	Survived
C-7	29	1140	F	0.8	0.12	89	112	39	17	bilateral ptx severe BPD	Survived
C-8	29	1200	M	0.65	0.24	67	77	32	13.2	Lt ptx	Survived
C-9[b]	29	1400	M	0.65	0.23	67	91	37	14.6	—	Survived
Mean (± SEM)	28.5 (.3)	1153 (71)	—	0.66 (0.05)	0.23 (0.02)	64 (5.8)	82.7 (6.7)	35.8 (1.1)	15.1 (1.5)	—	—
Difference between HFO-A and CMV	NS	NS	—	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	NS	—	—

[a]Data not included in statistical analysis.
[b]Twins.
NS, not significantly different.

Table 5. Pulmonary Complications in Infants with RDS ≤29 Weeks

	HFO-A	CMV
BPD	0	2
PDA (requiring surgical ligation)	0	1
PIE (severe on x-ray)	0	4
Pneumothorax	2	7
Pulmonary hemorrhage	1	0
Irreversible hypoxia	1	3
Total	4	17

Abbreviations: BPD, bronchopulmonary dysplasia; PIE, pulmonary interstitial emphysema; PDA, patent ductus arteriosus.

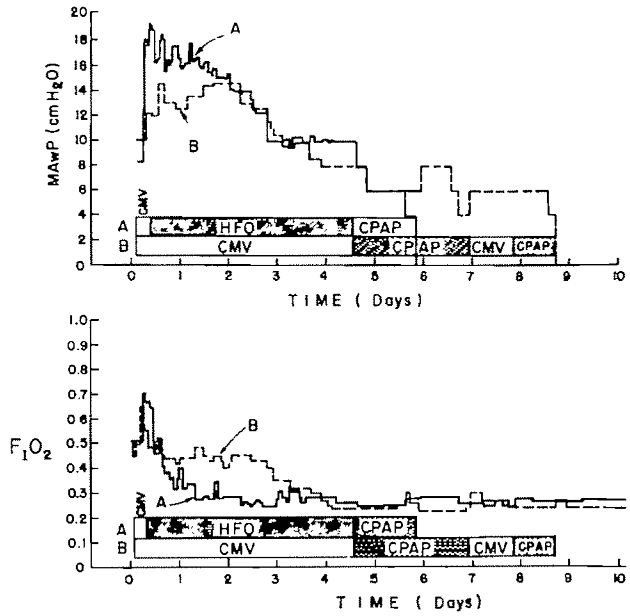

Figure 3. Superimposed profiles of MAwP and F_{IO_2} requirements of twin A (———), who was treated with HFO-A, and twin B (---) who was treated with CMV. Differences in MAwP are greatest over the first 24 hr of therapy, with MAwP levels becoming equal by 48 hr. F_{IO_2} requirements were higher initially in twin A, but decreased below those of twin B after 10 hr of ventilation by HFO-A.

inflations, there was no evidence of an increase in acute or chronic pulmonary complications. Pulmonary complications in infants with RDS are summarized in Table 5. There were a total of 17 complications in the nine CMV-treated infants and four in the six HFO-A-treated infants. There were two deaths among the six HFO-A-treated infants and three deaths in the nine infants treated with CMV.

The desired level of CO_2 elimination was always achieved using HFO-A, even preterminally under conditions of irreversible hypoxia. During CMV, Pa_{CO_2} levels of 70 and 86 mm Hg were recorded preterminally in the two infants for whom these values were available. CMV settings varied widely with individual needs. In mild disease settings such as 15/4 × 30 (PIP/PEEP × rate) were used. Pressures and rates were increased as needed to values such as 38/8 × 50 preterminally in severely affected infants.

Adequate humidification of inspired gases was readily achieved using this HFO-A system. No unusual tracheal pathology or inspissation of secretions was seen in the three HFO-A-treated infants who were autopsied.

Discussion

These data demonstrate that HFO-A merits further investigation as a form of primary ventilatory intervention for infants with RDS. Several questions need to be answered in a preliminary manner before large-scale trials of any new clinical device are attempted: 1) Is the new clinical device as effective as existing ones? 2) Is it as safe? 3) Does it introduce new hazards not present with the established therapy? This study provides preliminary answers to these questions. Adequate gas exchange was achieved in all infants in whom the primary diagnosis was IRDS. Therefore, the experimental ventilator is effective. Infant H-3, with extensive pneumonic consolidation, was not ventilated adequately by HFO-A within the pressure range we utilized during the terminal hours, but a trial of vigorous manual ventilation was also ineffective.

Ventilation using HFO-A also appeared to be acceptably safe in terms of acute and chronic barotrauma. Two CMV-treated infants developed BPD. Infant H-6 also developed BPD several days after being transferred from HFO-A to CMV. In view of the use of both ventilators, his outcome is hard to interpret. No infant treated solely with HFO-A developed BPD. In autopsies of infants who died with RDS, all three CMV-treated infants had extensive atelectasis, interstitial air dissection, and hyaline membrane formation by the time of death at 9–15 hr of age. Infant H-1 had only mild air dissection without hyaline membranes after 28 hr ventilation with HFO-A. Although these numbers are small, they suggest an acceptable degree of safety for the experimental mode. In these 11 cases, totaling over 800 hours of ventilation, no new hazards peculiar to the experimental ventilator became apparent. In particular, with the present system, adequate humidification was readily achieved, inspissation of secretions did not occur, and there was no evidence in cases that came to autopsy of the necrotizing tracheitis that has been reported using high-frequency jet ventilation in infants (2,4). It is im-

possible to conclude whether the single case of pulmonary hemorrhage (H-4), occurring in an infant with a bleeding diathesis who had received cardiopulmonary resuscitation, represents an incidental occurrence of a rare complication, or an event related in some way to the use of HFO-A. Since the risk of long-term neurologic and other deficits is high in the present study population and multifactorial in origin, the incidence of long-term complications cannot be conclusively addressed from such a small study.

The patterns of F_{IO_2} requirements reported in Table 4 are predictable considering the differences in MAwP settings, and therefore mean lung volumes, on the two ventilators. Boros et al. demonstrated that oxygenation in the atelectasis-prone lung was determined primarily by the mean transrespiratory pressure during CMV, both in premature lambs (15) and in infants with RDS (16). Marchak and associates (5) found the same relationship of oxygenation and MAwP during high-frequency oscillation of infants with RDS. Oxygenation consistently improved in these studies when higher levels of mean transrespiratory pressure were used to prevent alveolar collapse and maintain an adequate surface area for gas exchange. However, the early use of high MAwP during CMV has been limited by concerns about both acute and chronic barotrauma. Current practice places a high priority on keeping ventilator pressures as low as possible while still obtaining adequate gas exchange. Such principles reflect the cumulative experience of many centers, including reports in which the incidence of bronchopulmonary dysplasia appeared to be less when peak inspiratory pressures were kept below limits of 30 to 35 cm H_2O (17).

In contrast, the high ventilatory frequencies and small stroke volumes of HFO-A allow one to select an operating MAwP higher than one would routinely use with CMV while still keeping the peak inspiratory pressure <30 cm H_2O, since intratracheal pressure will fluctuate 4–8 cm H_2O above and below the mean value (5,18). Therefore, we could use an HFO-A protocol that gave a high priority to counteracting the collapsing tendency of the surfactant-deficient premature lung by using sustained inflation maneuvers to get the lung reexpanded, plus appropriate levels of MAwP to maintain it open, using oxygenation as a reflection of lung volume in this clinical setting. This protocol incorporates approaches developed in animal models of surfactant deficiency (8,9) and corroborated in premature animals (19).

The essential differences between current CMV treatment and the experimental HFO-A protocol are illustrated by Fig. 3, which shows the course of twins with RDS, one treated with CMV and the other with HFO-A, whose courses were similar to the group means of Table 3. In the CMV-treated twin MAwP levels started lower than the HFO-A treated one and did not reach maximal levels until an average of 37 hr. This time course is similar in pattern to that reported by Green et al. (20), who also found that MAwP levels tended to be highest about 36 hr of age, with MAwP reductions starting between 36–48 hr of age. Note that individual MAwP values in some of our more complicated cases exceed Green's 95 percentile limits since they deliberately excluded all infants with complicated disease courses from their data base. However, the overall pattern is very similar, with maximal ventilator pressures being reached on the second day, which is clinically taught to be the time of greatest severity of disease in uncomplicated IRDS. The maximum MAwP eventually needed during CMV did not differ significantly from the maximal MAwP levels used during HFO-A. However, during HFO-A this maximum was generally reached early (mean 5.2 hr) as in twin H-9, and was accompanied by an early fall in O_2 requirement while during CMV the maximal pressure settings were reached much later (mean 35.8 hr) and higher O_2 requirements were significantly more prolonged (F_{IO_2} not <0.4 until 64 hr during CMV).

In theory, a more balanced experimental design would have been produced by using CMV at the same early high MAwP levels as HFO-A. However, currently such a protocol would not be ethically acceptable in light of the reported link between high peak inspiratory pressure on CMV and the occurrence of BPD. Also to date all surfactant deficient rabbits in whom we have tried to use such a protocol with CMV have died of severe barotrauma, at levels of MAwP that were still too low to achieve the lung volume and oxygenation targets that were easily attained using HFO-A (21). The experience of Kolton et al. was similar (8). Similarly, 15 sec sustained inflations were not used during CMV because neither we nor Kolton have been able to demonstrate any benefit from such maneuvers in animals during CMV. Therefore, the use of SIs during CMV would represent risk without benefit and was not judged ethically or scientifically appropriate.

This study was stopped after enrolling only 11 HFO-A-treated cases because an ethical tension was developing. Despite the small numbers, statistically significant differences in inspired oxygen requirements were evident. Those differences were simply the expression of fundamental physiologic principles, namely, the improvement of oxygenation in the atelectasis-prone lung at higher transrespiratory pressures—pressures that could be used with acceptable safety during HFO-A. There was no reason to expect

that this fundamental physiologic principle would change with larger numbers. The study had already provided enough data to establish that HFO-A was a reasonable option for primary therapy of infants with respiratory failure in terms of basic safety and gas exchange efficacy. However, other lines of investigation were starting to raise new questions about the mechanisms of lung injury in the atelectasis-prone lung. There was reason to ask whether one should pursue high lung volumes and early decreases in F_{IO_2}, or lower lung volumes (and, therefore, pressures) and delayed decreases in F_{IO_2}. That question could not be answered readily in babies because of biologic variability. It was amenable to testing in the animal laboratory. Therefore, we decided to curtail clinical studies temporarily and do the necessary animal studies to help determine the optimal protocol for further clinical use of HFO-A (21). We felt this course of action would expose further humans to study only when as many unknowns as possible had been resolved by systematic animal investigation.

We found that the sustained inflations introduced to HFO-A by Kolton et al. in animal models (8) also reverse atelectasis early in the course of human IRDS, and facilitate early reductions in F_{IO_2} if used with a MAwP sufficient to keep the lung reexpanded. Our SI maneuver differed from that used in Kolton et al. (8) and Hamilton et al's. (9) animal studies, in which the oscillator was turned off while increasing airway pressure to 30 cm H_2O for 15 secs. In surfactant-deficient rabbits we found that a target Pa_{O_2} level could be achieved at a MAwP at least 5 cm H_2O lower, when an SI was performed with the ventilator left on as compared with an SI with the ventilator turned off (18). We have, therefore, adopted this approach to volume recruitment since the lower MAwP is less likely to impair cardiac output and the risk of barotrauma is theoretically less.

We used a fixed HFO-A rate more for practical than theoretical reasons. At present, there is no clear rationale that would allow one to select a rate of 15 as opposed to 10, 20, or even 30 Hz. However, we have considerable experience, both human and animal, at 15 Hz and know that HFO-A is effective at that frequency. From a practical standpoint, it becomes much easier to use chest wall motion to gauge the appropriate stroke volume for a given infant, if one uses a fixed ventilator rate.

Some aspects of clinical care are more difficult during HFO-A. Neither air entry nor heart sounds can be assessed by auscultation during HFO-A. Therefore, electronic monitors of cardiac function must be relied upon more exclusively. For auscultation purposes we simply stop HFO-A and ventilate the infant briefly with an ancillary system. However, we encourage nurses to hand-ventilate the infants only when necessary since O_2 requirements generally increase during such periods. Patient discoordination with the ventilator was never a problem during HFO-A, unlike our experience with CMV during which muscle paralysis must sometimes be used to permit effective conventional ventilation. If patients were deliberately hyperventilated during HFO-A (as for attempted reversal of extrapulmonary shunting) they became apneic. Otherwise they generally maintained spontaneous efforts at rates of 20–92 breaths per minute with the high-frequency oscillations superimposed.

We conclude that HFO-A, used as a primary form of ventilatory support in IRDS, demonstrates sufficient efficacy and safety to warrant further larger scale trials of this therapy.

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Cerebral Autoregulation and Flow/Metabolism Coupling during Cardiopulmonary Bypass: The Influence of Pa_{CO_2}

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MURKIN JM, FARRAR JK, TWEED WA, McKENZIE FN, GUIRAUDON G. Cerebral autoregulation and flow/metabolism coupling during cardiopulmonary bypass: the influence of Pa_{CO_2}. Anesth Analg 1987;66:825–32.

Measurement of ^{133}Xe clearance and effluent cerebral venous blood sampling were used in 38 patients to determine the effects of cardiopulmonary bypass, and of maintaining temperature corrected or noncorrected Pa_{CO_2} at 40 mm Hg on regulation of cerebral blood flow (CBF) and flow/metabolism coupling. After induction of anesthesia with diazepam and fentanyl, mean CBF was 25 ml·100 g^{-1}·min^{-1} and cerebral oxygen consumption, 1.67 ml·100 g^{-1}·min^{-1}. Cerebral oxygen consumption during nonpulsatile cardiopulmonary bypass at 26°C was reduced to 0.42 ml·100 g^{-1}·min^{-1} in both groups. CBF was reduced to 14–15 ml·100 g^{-1}·min^{-1} in the non-temperature-corrected group (n = 21), was independent of cerebral perfusion pressure over the range of 20–100 mm Hg, but correlated with cerebral oxygen consumption. In the temperature-corrected group (n = 17), CBF varied from 22 to 32 ml·100 g^{-1}·min^{-1}, and flow/metabolism coupling was not maintained (i.e., CBF and cerebral oxygen consumption varied independently). However, variation in CBF correlated significantly with cerebral perfusion pressure over the pressure range of 15–95 mm Hg. This study demonstrates a profound reduction in cerebral oxygen consumption during hypothermic nonpulsatile cardiopulmonary bypass. When a non-temperature-corrected Pa_{CO_2} of approximately 40 mm Hg was maintained, CBF was lower, and analysis of pooled data suggested that CBF regulation was better preserved, i.e., CBF was independent of pressure changes and dependent upon cerebral oxygen consumption.

Key Words: ANESTHESIA—cardiovascular. BRAIN—blood flow, metabolism. SURGERY—cardiac.

An estimated 200,000 surgical procedures are performed using cardiopulmonary bypass (CPB) each year in North America (1). Despite an advancing age and increased incidence of cerebrovascular disease in the surgical population, cerebrovascular responses attending CPB are only poorly understood. The majority of cardiac surgical procedures are carried out using hypothermic CPB at average temperatures of 26–30°C. Under these conditions the influence of various techniques for acid–base management during hypothermic CPB and the impact of changes in Pa_{CO_2} on cerebral blood flow regulation and flow/metabolism coupling are unknown. Both the optimal management of acid–base status as determined by CO_2 tension and the lower limit of cerebral autoregulation during hypothermic CPB are unclear.

Recent studies examining cerebral blood flow (CBF) during CPB have yielded contradictory data and have resulted in conflicting recommendations regarding the lowest acceptable perfusion pressure (2–6). Some of these studies have demonstrated the apparent failure of cerebral autoregulation below a mean arterial pressure (MAP) of 55 mm Hg (2–4) and increases in CBF to 65 ml·100 g^{-1}·min^{-1} during hypothermic CPB (4). Others have reported maintenance of cerebral autoregulation at an MAP of 30 mm Hg and a mean CBF ranging from 9 to 13 ml·100 g^{-1}·min^{-1} (5,6). The patient populations and CBF methodologies were comparable in these series; the primary difference was in the management of Pa_{CO_2} during hypothermic CPB. Because the cerebral metabolic rate for oxygen (CMR_{O_2}) was not examined, the adequacy of CBF, or the influence of changes in CO_2 on cerebral flow/metabolism coupling, could not be directly assessed. The present study was therefore designed to investigate the influence of CPB on CBF and CMR_{O_2}, and to determine the optimal management of acid–base and Pa_{CO_2} dur-

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ing hypothermic CPB for preservation of cerebral autoregulation and flow/metabolism coupling.

Methods

After approval from the Hospital Committee on Human Research and after obtaining written consent, 38 patients undergoing elective coronary artery bypass surgery were investigated. Cerebral blood flow and $CMRO_2$ were measured both before and after CPB as well as twice during hypothermic CPB and once during normothermic CPB. The progressive rise in MAP seen during the hypothermic phase of nonpulsatile CPB enabled the two CBF measurements to be made at differing perfusion pressures as an indicator of cerebral autoregulation. Measuring CBF during normothermic CPB evaluated the effect of nonpulsatile flow on CBF and $CMRO_2$.

Because of an initial unfamiliarity with the technique of non-temperature correction during hypothermic CPB, patients were not randomized into two study groups. Rather, the first group of 17 patients was managed according to our standard protocol (temperature-corrected group). Arterial gas tensions, measured at 37°C, were temperature-corrected using standard formulas (Blood Gas Calculator, Radiometer), and exogenous CO_2 was added to the pump oxygenator as necessary to maintain a temperature-corrected $PaCO_2$ of approximately 40 mm Hg (7). In the absence of metabolic derangements, this approach, termed pH-stat management, produces a nearly constant pH of 7.4 at all temperatures (8). In the next 21 patients, a non-temperature-corrected $PaCO_2$ of approximately 40 mm Hg was maintained during hypothermic CPB (non-temperature-corrected group). This has been designated α-stat management because it maintains a constant buffering capacity of α-imidazole resulting in a relative respiratory alkalosis during hypothermia (8). These two patient groups were otherwise identical, both demographically (Table 1) and with respect to intraoperative management. All patients were without evidence of cerebrovascular disease or diseases that affect cerebrovascular autoregulation, e.g., untreated hypertension, diabetes mellitus.

Patients were premedicated with 0.10 mg/kg morphine IM, 0.006 mg/kg scopolamine IM, and 0.15 mg/kg oral diazepam in addition to their chronic antianginal medications (Table 1). Anesthesia was induced and maintained with 0.1 mg/kg fentanyl, 0.5 mg/kg diazepam, and oxygen. During CPB, a nonpulsatile pump flow of 2.0–2.5 $L{\cdot}m^{-2}{\cdot}min^{-1}$ was maintained using an unfiltered arterial line and membrane oxygenator (Cobe CML). In addition to intraarterial manometry, a thermodilution pulmonary artery catheter, and continuous ECG monitoring, the intraoperative electroencephalogram (EEG) was continuously recorded on a 10-channel electroencephalograph (Nihon Kohden) using a 10–20 parasagittal block montage (9) with a passband of 0.5–70 Hz, time constant 0.3 sec, and sensitivity 7 mm/50 μV. Effluent cerebral venous blood was sampled from a 15-cm 16-Fr catheter introduced percutaneously and threaded retrograde into the right jugular bulb. Appropriate location of the jugular bulb catheter was heralded in the awake patients by a complaint of transient discomfort in the ipsilateral ear. Postoperative confirmation of the appropriate location of the catheter was obtained by x-rays of the skull in 13 patients, or by noting its cephalad direction on chest x-ray in the remainder. Cerebral perfusion pressure (CPP) was calculated as MAP minus cerebral venous pressure with all hemodynamic transducers referenced to atmosphere at the level of the external auditory meatus. The modified Glasgow coma scale was used postoperatively in the intensive care unit to record times until awakening, responsiveness, and extubation.

Table 1. Comparison of Patient Groups[a]

	Temperature-corrected group	Non-temperature-corrected group
Age (yr)	53 ± 8	56 ± 10
Duration of CPB (min)	109 ± 34	104 ± 19
Time until extubation (hr)	18.3 ± 3.5	17.4 ± 3.9
Female/male	2/15	5/16
β-Blocker[b]	12/17	16/21
Calcium blocker[b]	13/17	13/21
Nitrates[b]	12/17	16/21

[a]Mean ± SD.
[b]Ratio of patients in each group receiving chronic medications.

Cerebral blood flow measurements were determined from the clearance of xenon radioisotope (^{133}Xe) using a 10-channel cerebrograph (Novo Diagnostics 10a). Measurements before and after CPB were obtained by IV injection of 6 mCi of ^{133}Xe in saline using end-tidal respiratory gas sampling to correct for recirculation. Cerebral blood flow during CPB was determined by the injection of 6 mCi of ^{133}Xe into the arterial port of the pump oxygenator. Preliminary studies did not detect recirculation of ^{133}Xe, and therefore an intraarterial analysis mode was used for calculation of CBF during CPB. The resulting ^{133}Xe clearance curves were assessed by noncompartmental height-over-area analysis (10), which is less sensitive to shifts in compartment size, "slippage," such as can occur in pathologic tissue or under extreme physiologic conditions (11). This represents the mean flow

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Table 2. Measurements during Cardiopulmonary Bypass

	After induction (1)	Hypothermic CPB_{15} (2)	Hypothermic CPB_{30} (3)	Normothermic CPB (4)	After CPB (5)
n (+)	15	13	13	14	14
n (−)	15	16	16	18	16
Temperature	35.3 ± 0.4	25.5 ± 1.7^{g}	26.1 ± 1.5^{g}	36.7 ± 1.0^{f}	$35.8 \pm 0.$[illegible]
(°C)	35.3 ± 0.8	27.1 ± 0.9^{g}	27.5 ± 1.0^{g}	37.1 ± 0.5^{g}	$35.9 \pm 0.$[illegible]
CPP	75 ± 11	46 ± 19^{g}	66 ± 11	58 ± 9^{f}	70 ± 10
(mm Hg)	66 ± 11^{b}	46 ± 17^{f}	75 ± 19	58 ± 16	67 ± 13
$Paco_2$[a]	36.6 ± 4.5	38.4 ± 5.6	40.9 ± 5.1^{c}	35.3 ± 3.8	$38.4 \pm 3.$[illegible]
(mm Hg)	34.3 ± 3.6	$27.4 \pm 2.3^{d,f}$	$26.2 \pm 2.9^{d,f}$	35.4 ± 6.1	$36.3 \pm 2.$[illegible]
MAP	80 ± 6	54 ± 14^{g}	76 ± 12	66 ± 10^{f}	81 ± 11
(mm Hg)	74 ± 12	53 ± 15^{f}	80 ± 16	66 ± 14	76 ± 12

Intergroup difference (+) CO_2 group vs (−) CO_2 group; [a]Corrected to patient temperature; [b]$P < 0.05$; [c]$P < 0.005$; [d]$P < 0.001$.
Intragroup differences vs after induction (1): [e]$P < 0.05$; [f]$P < 0.01$; [g]$P < 0.001$.
Abbreviations: CPP, cerebral perfusion pressure. (+), temperature-corrected $Paco_2$ = 40 mm Hg (pH-stat); (−), measured $Paco_2$ = 40 mm Hg (α-stat)

of all tissue seen by a detector and includes a small extracerebral component in addition to cerebral white and grey matter. Integration of the curve to 15 min rather than infinity reduces the effect of the extracerebral component (11). Because the solubility of ^{133}Xe varies inversely with temperature and directly with hematocrit, standard correction factors for changes in xenon partition coefficient due to alterations in temperature and hemoglobin were applied to the raw counts, and the clearance curves were recalculated (12). Mean hemispheric CBF was calculated as the average of the regional CBF from all five detectors ipsilateral to the jugular bulb catheter and was used in the calculation of $CMRo_2$ (13).

$CMRo_2$ was determined from the product of mean hemispheric CBF and the arterial-jugular oxygen content difference. Oxygen content was calculated as the sum of the O_2 in solution, determined from the temperature-corrected Pao_2 as measured on Radiometer ABL 2, and the product of the O_2 saturation as measured on an OSM 3 Hemoximeter and the hemoglobin concentration measured on a Colter S+2.

Intergroup demographic data, including prevalence and type of preoperative medications, and sex ratio were analyzed using the χ^2 test. Age comparisons, duration of CPB, and times until extubation were analyzed using an unpaired two-tailed t-test. Statistical significance of intragroup hemodynamic data was tested using one-way ANOVA with Dunnett's test comparing measurements against control (after induction). Intergroup hemodynamic comparisons were made using an unpaired two-tailed t-test. For identification of significant variables, multiple stepwise linear regression analysis using the method of ordinary least squares regressed $CMRo_2$, $Paco_2$, Cao_2, and CPP against CBF during hypothermic CPB. Fo[illegible] purposes of comparison, simple linear regression wa[illegible] used to compare the influence of $CMRo_2$ and CP[illegible] against CBF in the temperature-corrected and non corrected groups. For all analyses $P < 0.05$ was con sidered significant.

Results

A total of 150 complete CBF measurements were mad[illegible] in 38 patients. A number of CBF measurements fro[illegible] patients in both groups were excluded from some o[illegible] the five events examined due to unsatisfactory ^{133}X[illegible] clearance curves. The majority of these resulted whe[illegible] background activity exceeded 10% of the peak activ ity. Data entries for each event in Table 2 are thu[illegible] comprised of only patients in whom satisfactory clear ance curves were obtained for that event.

Patient Demographics

There were no significant differences between group[illegible] with respect to age, sex, preoperative medications duration of CPB, or time until extubation (Table 1) Similarly, MAP, CPP, and temperature were com parable between groups at all times during CPB (Tabl[illegible] 2). Mean times to awakening and extubation wer[illegible] similar in both groups, and no neurologic deficits wer[illegible] detected. In the temperature-corrected group, two pa tients died within 24 hr after surgery. One patien[illegible] died of circulatory failure compounded by cardia[illegible] tamponade, and the other died from a low outpu[illegible] state despite an intraaortic assist device and inotropi[illegible] support. In the non-temperature-corrected group on[illegible]

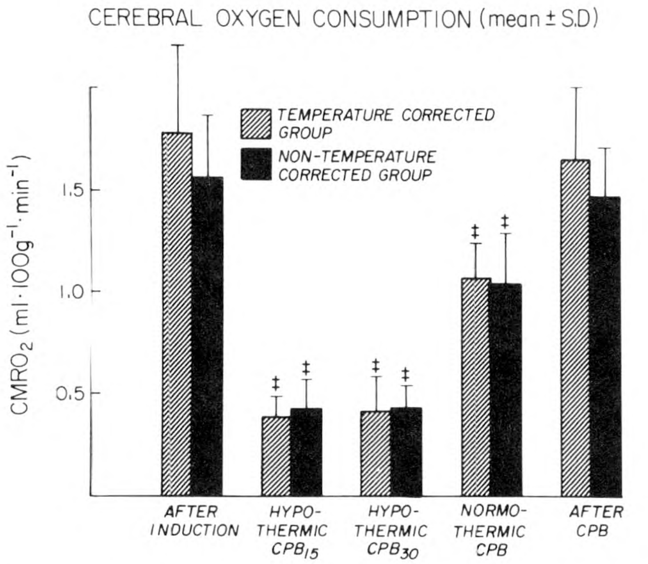

Figure 1. Cerebral oxygen consumption in temperature-corrected and non-temperature-corrected groups. No significant differences in $CMRO_2$ occur between groups at any time. $CMRO_2$ is profoundly reduced during hypothermic CPB and remains significantly reduced in both groups during normothermic CPB. $CMRO_2$, cerebral metabolic rate for oxygen; CPB, cardiopulmonary bypass. ‡ indicates values within each group compared to control (after induction) for which $P < 0.001$.

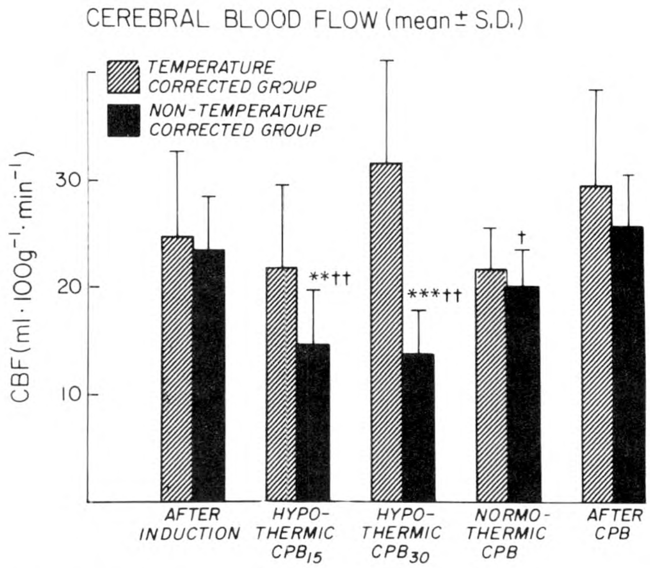

Figure 2. Cerebral blood flow in temperature-corrected and non-temperature-corrected groups. A significant difference in CBF between groups occurs only during hypothermic CPB. CBF, cerebral blood flow; CPB, cardiopulmonary bypass. ** indicates values between groups for which $P < 0.005$; *** indicates $P < 0.001$. † marks values within each group compared to control (after induction) for which $P < 0.05$; †† indicates $P < 0.01$.

patient died 24 hr postoperatively from sudden onset of refractory ventricular fibrillation.

Cerebral Oxygen Consumption

There were no differences in $CMRO_2$ between groups at any time (Fig. 1). After induction of anesthesia, the average $CMRO_2$ was 1.67 ml·100 g^{-1}·min^{-1}, whereas after weaning from CPB it was 1.55 ml·100 g^{-1}·min^{-1}. During hypothermic CPB there was a significant reduction of $CMRO_2$ averaging 0.42 ml·100 g^{-1}·min^{-1} ($P < 0.001$) at a mean nasopharyngeal temperature of 26.6°C. After rewarming on CPB, $CMRO_2$ was still significantly reduced at 1.05 ml·100 g^{-1}·min^{-1} ($P < 0.001$).

Cerebral Blood Flow

In neither group did CBF differ significantly between the pre- and post-CPB measurements, averaging 25 ml·100 g^{-1}·min^{-1}. During hypothermic CPB, however, a highly significant difference between groups was apparent (Fig. 2). In the temperature-corrected group, the mean temperature-corrected $PaCO_2$ was 40 mm Hg. Cerebral blood flow in this group varied between 21.9 and 31.6 ml·100 g^{-1}·min^{-1}. By stepwise multiple linear regression analysis of pooled data, CBF was independent of $CMRO_2$, $PaCO_2$, and CaO_2, correlating only with CPP over the range from 15 to 95 mm Hg (CBF = 8.9 + 0.32 CPP; $n = 26$, $r = 0.59$, $P < 0.001$). In the non-temperature-corrected group, the mean temperature-corrected $PaCO_2$ was 27 mm Hg, and CBF was grouped between 13.8 and 14.7 ml·100 g^{-1}·min^{-1}. In this group multiple linear regression showed no correlation between CBF and CPP over the range from 20 to 100 mm Hg, but CBF was significantly correlated with $CMRO_2$ ($P < 0.02$) and CaO_2 ($P < 0.02$) (CBF = 20.4 + 12.3 $CMRO_2$ − 0.98 CaO_2; $n = 32$, $r = 0.63$, $P < 0.001$). In Figure 3, simple linear regression was used to further illustrate the differences between groups. In the temperature-corrected group, CBF was independent of $CMRO_2$ ($r = -0.11$, $P > 0.2$), but a highly significant correlation with CPP was shown (CBF = 8.9 + 0.3 CPP; $n = 26$, $r = 0.59$, $P < 0.002$). The non-temperature-corrected group demonstrated exactly the opposite relationships. CBF was significantly correlated with $CMRO_2$ (CBF = 7 + 16 $CMRO_2$; $n = 32$, $r = 0.50$, $P < 0.005$) but not correlated with CPP ($r = -0.16$, $P > 0.2$). During normothermic CPB, CBF was similar in both groups and was significantly reduced compared to that prior to CPB. At this time CBF correlated with $CMRO_2$ and CaO_2 (CBF = 19.8 + 6.4 $CMRO_2$ − 1.3 CaO_2; $r = 0.58$, $P < 0.05$).

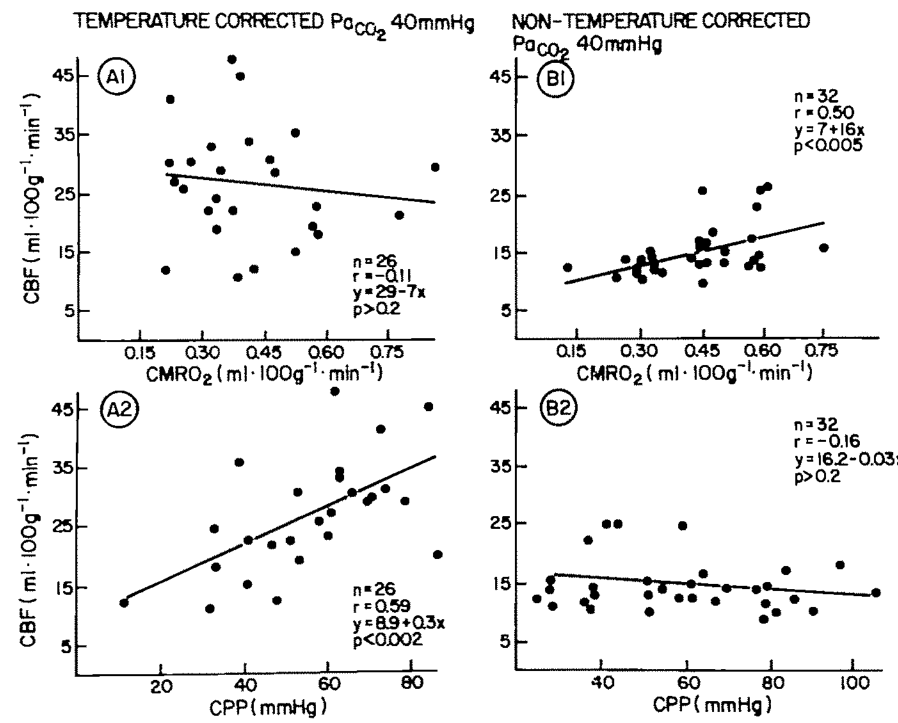

Figure 3. Simple linear regression of cerebral blood flow versus cerebral perfusion pressure or cerebral oxygen consumption for temperature-corrected and non-temperature-corrected groups. **Upper panel:** There is no significant correlation between CBF and $CMRO_2$ in the temperature-corrected group (**A1**), whereas CBF significantly correlates with $CMRO_2$ in the non-temperature-corrected group (**B1**). **Lower panel:** CBF is significantly correlated with CPP in the temperature-corrected group (**A2**), whereas CBF is independent of CPP in the non-temperature-corrected group (**B2**). CBF, cerebral blood flow; CPP, cerebral perfusion pressure; $CMRO_2$, cerebral metabolic rate for oxygen.

Electroencephalogram

There were no significant differences in EEG responses between groups. During hypothermic CPB there was a reduction in amplitude of the EEG activity resulting in low-frequency, low-voltage activity. With rewarming, the pattern was similar to that seen after induction of anesthesia, primarily low-frequency, high-voltage activity characteristic of high-dose narcotic anesthesia (14).

Discussion

Cerebral Autoregulation

Certain organs (notably the brain, kidney, and heart) have the ability to autoregulate, maintaining adequate blood flow and a normal oxygen supply/demand ratio despite a wide range of perfusion pressures. The brain regulates CBF according to local metabolic needs, maintaining tight regional flow/metabolism coupling. In the intact individual, CBF is constant over a range of MAP from approximately 60 to 150 mm Hg (15). Failure of autoregulation occurs with either intracerebral pathology or direct cerebral vasodilators, most notably CO_2 (16).

The two most common modes of acid–base management during hypothermic CPB involve maintaining either a temperature-corrected Pa_{CO_2} of 40 mm Hg (usually by addition of exogenous CO_2 to the pump oxygenator) or a non-temperature-corrected Pa_{CO_2} of 40 mm Hg (17). Over the past 20 yr, the temperature-corrected method has been most commonly used, and approximately 63% of perfusionists currently use this approach (M. Kurusz, Chairman, American Academy of Cardiovascular Perfusionists, personal communication). Given an average temperature of 27°C during hypothermia, the difference in Pa_{CO_2} between the two modes is approximately 20 mm Hg. Several investigators have shown CO_2 to be a potent cerebral vasodilator during nonpulsatile hypothermic CPB (6,18).

In the current study, both groups demonstrated a reduction in $CMRO_2$ to less than 25% of the level before CPB, at a temperature of 27°C. An identical $CMRO_2$ was observed in both groups despite a two-fold variation in CBF, implying that in neither group was cerebral oxygen consumption flow limited. The validity of the methodology for measuring $CMRO_2$ can be inferred from the consistency of our results with those of other investigators. The mean values of CBF and $CMRO_2$ we observed after induction of anesthesia, 25 ml·100 g^{-1}·min^{-1} and 1.67 ml·100 g^{-1}·min^{-1}, respectively, are similar to those reported by Vernheit et al. using a similar ^{133}Xe clearance technique in eight normal subjects after fentanyl/diazepam/N_2O anesthesia (19). These data also are consistent with animal studies using radiolabeled microspheres and demonstrating a 35–50% reduction in $CMRO_2$ and CBF produced by high-dose fentanyl administration in rats (20).

In the group in which a temperature-corrected Pa_{CO_2}

of 40 mm Hg was maintained, analysis of pooled data suggested that CBF was pressure-dependent, but independent of Pa_{CO_2}, CMR_{O_2}, or Ca_{O_2}. Similar results have been reported by other investigators. Henriksen et al. utilized similar acid–base management and measured an average CBF of 64 ml·100 g^{-1}·min^{-1} (4). They also found CBF to be independent of Pa_{CO_2} but varying with MAP below 55 mm Hg ($P < 0.01$). They concluded that cerebral autoregulation was lost below that level. Another recent study of humans using indirect estimates of CBF based upon a transcranial Doppler method to measure flow velocity through the middle cerebral artery also maintained a temperature-corrected Pa_{CO_2} of approximately 40 mm Hg (2). They similarly observed pressure-passive cerebral perfusion and concluded that cerebral autoregulation is impaired during nonpulsatile CPB. These studies are consistent with the known potent vasodilatory properties of CO_2. Elevation of CO_2 to maintain a temperature-corrected Pa_{CO_2} of approximately 40 mm Hg during hypothermia produces passive cerebral vasodilation, thus overriding cerebral vascular response to pressure changes.

In the group in whom a non-temperature-corrected Pa_{CO_2} of 40 mm Hg was maintained, pooled CBF was significantly correlated with CMR_{O_2} and Ca_{O_2} but did not correlate with CPP over the range from 20 to 100 mm Hg. This is also similar to the results obtained by others (5,6), who reported CBF ranging from 9.1 to 13.3 ml·100 g^{-1}·min^{-1} using a similar ^{133}Xe clearance technique during hypothermic CPB. Govier et al. found only a weak correlation between CBF and MAP and concluded that CBF is independent of perfusion pressure and that the lower limit of cerebral autoregulation appears to be an MAP of 30 mm Hg (5).

The present results demonstrate that at the lowered cerebral metabolic rate during hypothermia, a much lower cerebral blood flow is required to maintain adequate cerebral perfusion. When a non-temperature-corrected Pa_{CO_2} of 40 mm Hg is maintained (i.e., keeping total CO_2 constant at all temperatures) (8), CBF appear to be independent of CPP down to a pressure of 20 mm Hg.

Nonpulsatile CPB

During nonpulsatile CPB, other factors are also operative. The ratio of oxygen consumptions over a 10°C temperature change (Q10), determined for whole body oxygen consumption during hypothermic CPB in humans, is estimated at 2.72 (21). In our patients one would anticipate a reduction in CMR_{O_2} to approximately 37% of the original rate, i.e., the average CMR_{O_2} of 1.67 before CPB would be predicted to decrease to 0.61 ml·100 g^{-1}·min^{-1}. We observed a CMR_{O_2} of 0.39–0.43 ml·100 g^{-1}·min^{-1} during hypothermic CPB, i.e., 30% less than predicted. The internal consistency of our data is supported by the fact that a very similar CMR_{O_2} was observed in both groups despite a two-fold variation in CBF (Fig. 1). This also suggests that the low CBF in the non-temperature group is appropriate for the lowered CMR_{O_2}. The average CMR_{O_2} during normothermic CPB, 1.05 ml·100 g^{-1}·min^{-1}, is also more than 30% lower than the average CMR_{O_2} of 1.55 ml·100 g^{-1}·min^{-1} measured after separation from CPB. These observations suggest that nonpulsatile CPB per se has an effect on CBF and CMR_{O_2}, reducing both by approximately 30%.

This observed reduction in CMR_{O_2} of approximately 30% during CPB is confirmed from animal data. Creech et al. (22) observed a 50% reduction in CMR_{O_2} in normothermic dogs during nonpulsatile CPB. In another study of hypothermic dogs maintained on nonpulsatile CPB at 20°C, a 94% reduction in CMR_{O_2} was observed. Upon rewarming to 38°C during normothermic CPB, there was still a significant reduction in CBF of 24%, whereas CMR_{O_2} was reduced by 20% from the control measurements made prior to CPB (23). More recent investigations of CBF and cerebral glucose consumption (CMRglu) during normothermic CPB in pigs have demonstrated a 30% reduction in CMRglu after 3 hr of either pulsatile or nonpulsatile CPB, with uncoupling of CBF from CMRglu occurring in the nonpulsatile group (24).

Branthwaite has used a jugular thermodilution technique in humans to measure changes in CBF and CMR_{O_2} during the initial 5 min of normothermic CPB (25). Because of the methodology, only a qualitative assessment of the changes could be made, but it was concluded there was a marked reduction in CBF in 50% of patients studied and that there was considerable depression of cerebral metabolism. This was ascribed to a reduction in cerebral perfusion pressure. We have also observed an average 30% reduction in CMR_{O_2} during nonpulsatile normothermic CPB in patients undergoing arrhythmia surgery at a constant level of isoflurane anesthesia (26). Nonpulsatile perfusion also has been shown to reduce hepatic blood flow by 40%, as measured by indocyanine green clearance (27).

The mechanism of the observed reduction in CBF and CMR_{O_2} during nonpulsatile CPB remains speculative. Possible explanations include a primary reduction in tissue metabolism with secondary fall in CBF, impaired diffusion of oxygen to tissue, or uneven regional distribution of cerebral flow. Pulsatile flow may assist in the diffusion of metabolites between capillaries and tissues by reopening capillary

beds, enhancing lymph and interstitial flow, and by increasing kinetic diffusion (28). Loss of these mechanisms during nonpulsatile CPB thus may impair nutrient diffusion. Uneven regional cerebral blood flow due to altered myogenic contractility of cerebral arterioles also may be a factor (24). This remains an area for future investigation.

Clinical Implications

It is apparent from results in carotid artery surgery that unnecessary elevations of Pa_{CO_2}, although increasing global cerebral blood flow, do so at the expense of potentially ischemic areas, the so-called "steal phenomenon." Similarly, CO_2-induced cerebrodilation can critically reduce perfusion pressure within the circle of Willis, jeopardizing areas of brain dependent on flow through critically stenosed vessels (29). Clinical experience in over 60% of centers currently using a temperature-corrected CO_2 during hypothermic CPB suggests that for the average patient, the particular mode of acid–base management may not be crucial. There may, however, be subsets of patients, particularly those with cerebrovascular disease or derangements of cerebral autoregulation, in whom non-temperature-correction of Pa_{CO_2} may be advantageous by better preserving cerebral autoregulation. In addition, because cerebral emboli are felt to account for a significant proportion of neurologic deficits after CPB (30), any unnecessary elevation in CBF may further increase delivery of micro-emboli to the cerebral circulation. Demonstration of any clinically significant difference in outcomes or neurologic morbidity with differing modes of acid–base management during CPB will require prospective controlled trials.

Differences in acid–base management thus account for most of the variation in CBF data reported by other groups during hypothermic CPB. Maintaining a temperature-corrected Pa_{CO_2} at 40 mm Hg uncouples cerebral flow/metabolism and probably impairs cerebral autoregulation. During hypothermia, a non-temperature-corrected Pa_{CO_2} of 40 mm Hg maintains a more physiologic relationship between CBF and CMR_{O_2}, and cerebral autoregulation appears to be intact over a range of cerebral perfusion pressures from 20 to 100 mm Hg. Nonpulsatile CPB may also independently reduce CBF and CMR_{O_2}, but the etiology of these changes is currently unclear.

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Comparison of High-Frequency Jet Ventilation with Conventional Mechanical Ventilation for Bronchopleural Fistula

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BISHOP MJ, BENSON MS, SATO P, PIERSON DJ. Comparison of high-frequency jet ventilation with conventional mechanical ventilation for bronchopleural fistula. Anesth Analg 1987;66:833–8.

In seven patients with acute respiratory failure and a bronchopleural fistula, the authors compared gas exchange and volume of gas lost via the chest tube during conventional mechanical ventilation (CV) and high-frequency jet ventilation (HFJV). After the initial comparison, patients were randomized to HFJV or CV, unless one mode of ventilation was clearly superior based on preestablished criteria. In six of the seven patients, oxygenation deteriorated after the switch from CV to HFJV. The ratio of Pa_{O_2} *to* FI_{O_2} *declined from 227 ± 167 to 133 ± 100 (mean ± SD,* $P < 0.05$*), and the* Pa_{CO_2} *increased from 47 ± 13 to 56 ± 18 mm Hg (*$P < 0.05$*). The mean chest tube leak did not change significantly. Randomization of the mode of ventilation was not performed in any patient because CV was superior by a priori criteria. We conclude that when acute respiratory failure is complicated by a bronchopleural fistula, HFJV with mean airway pressures comparable to those provided during conventional ventilation does not provide satisfactory gas exchange.*

Key Words: VENTILATION—high frequency, intermittent positive pressure breathing.

One of the most promising potential uses of high-frequency jet ventilation (HFJV) has been in the patient with respiratory failure and a bronchopleural fistula (BPF) (1–3). Because of the high mortality associated with persistent BPF in patients with acute respiratory failure (4), we initiated a study to determine whether the fistula would close more rapidly in such patients if ventilated with HFJV in place of conventional mechanical ventilation (CV). We hypothesized that HFJV would lower peak flows across the fistula (5) and consequently speed closure of the fistula.

Methods

Patient Selection

We studied seven patients with acute respiratory failure who were receiving mechanical ventilation and had a persistent BPF demonstrated by an air leak persisting more than 24 hr after the insertion of a chest tube. Patients were consecutive cases meeting these criteria except for cases when either the family or the primary physician did not consent. Consent was obtained from the patients' nearest relative after procedures established in accordance with the Human Subjects Review Board of the University of Washington.

Protocol

After consent was obtained, we replaced the endotracheal tube with a Hi-Lo Jet Tracheal Tube (NCC Division, Mallinckrodt, Argyle, NY) to permit monitoring of distal tracheal pressures. Throughout the experiment, patients were monitored with an ear oximeter (Hewlett-Packard, Palo Alto, CA) to ensure that desaturation to unacceptable levels did not occur. Conventional ventilation consisted of mechanical ventilation using the tidal volume and positive end-expiratory pressure (PEEP) that had produced optimal gas exchange as defined by physicians caring for the patients. The mandatory rate was also set by the physicians in the case of patients receiving assisted mechanical ventilation (AMV). Patients being ventilated with intermittent mandatory ventilation were switched to AMV at a comparable minute ventilation. Baseline measurements were then made of arterial blood gas

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Table 1. Individual Patient Data

Patient data during conventional ventilation							
Patient Number	FI_{O_2}	V_t (ml)	Frequency (breaths/min)	$\dot{V}_E$ (L/min)	$\dot{V}_L$ (L/min)	PIP (cm H_2O)	Mean AP (cm H_2O)
1	1	750	10	3.4	14.4	30	15
2	0.7	950	22	20.9	0.76	58	22
3	1	650	35	19.2	5.65	64	22
4	1	850	45	42.5	8.37	70	28
5	0.6	650	50	20.4	14.0	78	33
6	0.7	1200	18	19.7	0.8	58	19
7	1	800	16	12.8	5.3	46	12
Mean	0.86	865	28	19.84	5.8	58	22
SD	0.17	162	14	10.92	4.68	15	7

Table 2. Individual Patient Data

Patient data during jet ventilation							
Patient Number	FI_{O_2}	Driving pressure (PSI)	Frequency (breaths/min)	$\dot{V}_E$ (L/min)	$\dot{V}_L$ (L/min)	PIP (cm H_2O)	Mean AP (cm H_2O)
1	1	14	100	13.4	14.5	18	15
2	0.7	30	100	50	0.89	32	22
3	1	20	100	19.2	8.15	42	24
4	1	20	100	35.8	11.1	38	27
5	1	39	100	—	—	48	27
6	0.7	23	100	29.7	0.53	30	20
7	1	18	60	21	6.8	28	11
Mean	0.91	23	94[a]	28.18[a]	7.00	34	21
SD	0.14	8	14	12.16	5.06	9	6

Abbreviations for both tables: V_t, Tidal volume; $\dot{V}_E$, exhaled minute ventilation; $\dot{V}_L$, leaked minute volume; PIP, peak inspiratory pressure; Mean AP, mean airway pressure; $P\bar{v}_{O_2}$, pulmonary venous P_{O_2}; $\dot{Q}_t$, cardiac output; PAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; BP, mean systemic blood pressure; HR, heart rate.
[a] $P < 0.05$ vs conventional ventilation. Pa_{O_2} not compared as FI_{O_2} varied.

tensions, heart rate, blood pressure, mean and peak airway pressures, and air leak through the BPF. Airway pressures were measured at the tracheal end of the multi-lumen endotracheal tube using the distal port. The port was situated 2–4 cm above the carina and its position confirmed by roentgenogram. Air leak was measured by collecting the output of the chest tube into a 120-L spirometer (Warren E. Collins, Braintree, MA), using a previously described method for measurement of leaked gas during HFJV (6). Minute ventilation expired via the endotracheal tube was determined by collecting expired gas into an evacuated latex atmosphere balloon (Kaysam Corporation, Totowa, NJ) which was then emptied into the 120-L spirometer. In patients with pulmonary artery catheters in place ($n = 5$), we also measured pulmonary artery pressure, pulmonary artery wedge pressure, cardiac output, and mixed venous blood gas tensions (Tables 1 and 2).

After baseline measurements, patients were then switched to HFJV and the measurements repeated after 30 min, although in patient number 5 they were repeated sooner due to obvious clinical deterioration. We used a prototype HFJV machine (Bear Medical Systems, Riverside, CA) set to a frequency of 100 except in patient number 7 when a rate of 60 was used at the request of the primary physician. Inspiratory time was set at 33%, and driving pressure was adjusted to provide a mean pressure in the distal trachea identical to that achieved during CV. A 16-gauge injector positioned at the endotracheal tube connector provided the jet flow. Entrained gas was supplied from a conventional ventilator circuit.

The protocol randomized patients after the trial of HFJV assuming that they did not meet one of three escape criteria: 1) Pa_{CO_2} increased to the extent that pH decreased to levels less than 7.30; 2) Pa_{O_2} decreased 20% below baseline levels; 3) volume leaked via the BPF increased 50% or more. In patients 3–7, before beginning the study, we increased FI_{O_2} as a safety precaution in case of hemoglobin desaturation during the trial. This precaution was initiated after

Table 1 (*continued*)

Pa_{O_2} (mm Hg)	Pa_{CO_2} (mm Hg)	pH	$P\bar{v}_{O_2}$ (mm Hg)	$\dot{Q}_t$ (L/min)	PAP (mm Hg)	PAWP (mm Hg)	BP (mm Hg)	HR (beats/min)
183	38	7.4	333	5.7	29	15	133	86
63	42	7.36	—	—	—	—	—	125
86	48	7.35	38	5.1	36	10	72	133
77	73	7.33	34	—	52	18	90	147
328	56	7.31	—	—	—	—	110	113
281	32	7.55	30	4.45	25	16	108	103
204	38	7.38	—	4.8	13	5	88	110
175	47	7.39	34	5.01	31	13	98	117
97	13	0.07	3	0.46	13	5	22	20

Table 2 (*continued*)

Pa_{O_2} (mm Hg)	Pa_{CO_2} (mm Hg)	pH	$P\bar{v}_{O_2}$ (mm Hg)	$\dot{Q}_t$ (L/min)	PAP (mm Hg)	PAWP (mm Hg)	BP (mm Hg)	HR (beats/min)
139	42	7.39	30	4.36	21	16	101	60
42	42	7.38	—	—	—	—	73	112
115	67	7.27	36	6.11	47	11	81	136
62	89	7.23	28	—	50	21	83	144
370	67	7.24	—	—	—	—	136	142
61	38	7.49	28	6.44	35	—	108	109
101	45	7.37	—	5.1	—	5	81	118
127	56	7.34*	31	5.50	38	13	88	113
104	18	0.09	3	0.82	11	6	12	27

substantial hemoglobin desaturation occurred in patient number 2 during HFJV. In all patients except numbers 5 and 7, PEEP was used during CV. The ventilator provided air flow as needed to maintain the set level of PEEP, resulting in net total air flow that in some patients exceeded the set minute ventilation. This was most marked in patient number 1 (Table 1) in whom airflow ($\dot{V}_E + \dot{V}_L$) was 17.8 L/min despite a tidal volume of 750 ml and a frequency of 10/min. Comparisons between HFJV and CV were performed using Student's *t*-test for paired samples.

Results

We studied a total of seven patients (Table 1). In five of the patients the BPF was a consequence of barotrauma occurring during mechanical ventilation for adult respiratory distress syndrome. One patient had a subsegmental bronchial tear after a motor vehicle accident. The tear had not been detected on a bronchoscopy prior to our study but was documented on a subsequent reexamination. Patient number 7 had a persistent BPF after pleural decortication.

Ventilatory settings are given in Tables 1 and 2.

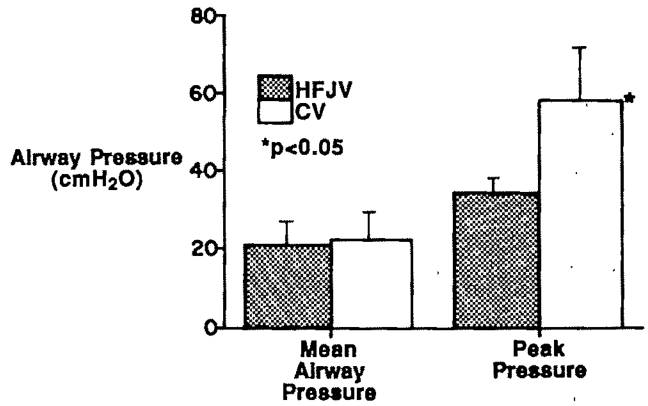

Figure 1. Mean airway pressures remained comparable during both modes of ventilation, but peak pressures were lower during HFJV ($P < 0.05$) ($n = 7$).

Mean airway pressures during HFJV and CV were comparable, but peak inspiratory pressures averaged 58 ± 6 cm H_2O during CV vs 34 ± 3 cm H_2O during HFJV ($P < 0.05$) (Fig. 1).

Leak size varied widely, ranging from 0.8 to 14.4 L/min during CV (Fig. 2A). The highest value oc-

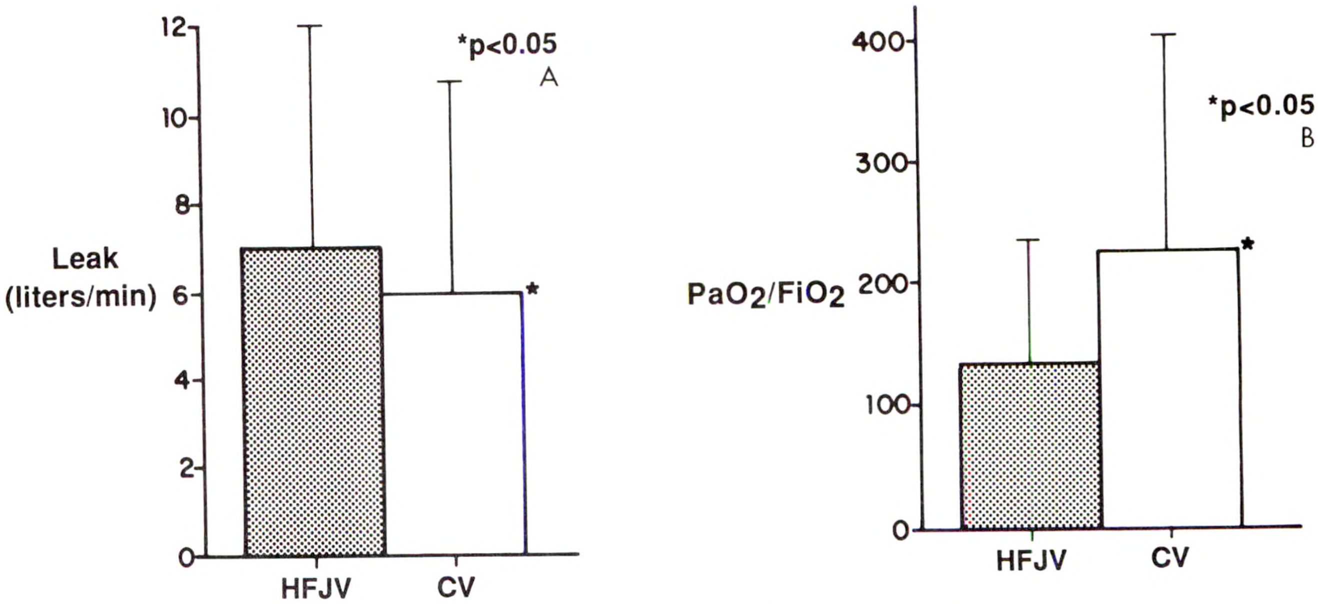

Figure 2. **A**) Leaked volume measured from chest tubes increased slightly but significantly during HFJV ($n = 6$). **B**) Gas exchange deteriorated during HFJV as demonstrated by a lower Pa_{O_2} to FI_{O_2} ratio and an increase in arterial Pa_{CO_2} ($n = 7$).

curred in the patient with a bronchial tear. Patients 3 and 4 each had multiple chest tubes, necessitating measuring the leak from each and then summing them. Leaks could not be compared in patient number 5 because of rapid deterioration during HFJV. Leaked volume decreased during HFJV by more than 20% in one patient (number 6). Substantial increases in leaked volume were seen in patients 3, 4, and 7, each of whom had a relatively large parenchymal leak. Patient number 1, who had an airway leak, showed no change in leaked volume with HFJV. In none of the patients did the relative leak volume meet our a priori condition of being 50% greater as a condition for being removed from randomization.

Because of substantial deterioration in oxygenation or carbon dioxide excretion after the initiation of HFJV, in no patient did randomization for long-term ventilation take place. Patient number 1, who had a bronchial tear, was relatively easily supported but did show a decrease in Pa_{O_2} great enough to exclude him from randomization. Patients 6 and 7 had marked deterioration in oxygenation after the initiation of HFJV, with rapid return to baseline levels after reinstitution of CV. Patients 3, 4, and 5, each of whom had markedly elevated physiologic dead space, developed increases in Pa_{CO_2} and decreases in pH which prevented randomization. The deterioration after the institution of HFJV was so rapid in patient number 5 that measurements of $\dot{V}_L$ and $\dot{V}_E$ could not be completed because of progressive tachycardia and hypertension. In general, oxygenation tended to deteriorate with HFJV despite comparable mean airway pressure, with the ratio of Pa_{O_2} to FI_{O_2} decreasing from a mean of 227 ± 63 to 133 ± 38 ($P < 0.05$) (Fig. 2B) after the transition from CV to HFJV. The most marked deterioration in Pa_{CO_2} occurred in patients in whom adequate CO_2 elimination had not been possible with CV. We saw no significant differences in cardiovascular function with the two modes of ventilation.

Discussion

Other investigators have documented that HFJV achieves adequate ventilation even in the face of massive air leaks (1–3,7). Whereas adequate ventilation is often an immediate priority when a large BPF is present, the ultimate goal is closure of the fistula. We hoped to test the hypothesis that HFJV would speed fistula closure by reducing the flow across it. We chose to match mean tracheal pressures between CV and HFJV because flow across a fistula is proportional to the pressure difference across it. Under the conditions studied, HFJV led, as defined by our a priori criteria, to gas exchange that was inferior to CV in all seven patients ($P < 0.05$).

Based on our experience and the experience of other investigators, in many of the patients we studied, adequate gas exchange could probably have been achieved with HFJV by altering the ventilator settings,

but at the cost of a higher mean airway pressure (8). Increased inspiratory time almost certainly would have improved oxygenation, and increased driving pressure would have increased CO_2 elimination, but either maneuver would have increased airway pressure. In patient number 5, driving pressure was maximal but still did not result in adequate CO_2 elimination.

While oxygenation during both CV and high-frequency ventilation appeared to correlate directly with mean airway pressures in this study, there was a deterioration in the PaO_2/FI_{O_2} ratio in all but one of our patients. We speculate that this resulted from the collapse of alveolar units during HFJV, a problem that has been preventable in animal models ventilated at higher frequencies by the use of intermittent sustained inflations (9).

The lack of a decrease in the volumes leaked via the BPF that we observed was disappointing in view of our original hypothesis. However, an examination of the theoretical explanations for decreased leak during HFJV suggests that it will be less likely to have a marked effect when a peripheral leak is combined with severe injury and decreased compliance in the remainder of the parenchyma than when only an airway is disrupted. Leaked volume may decrease with increased frequency and lowered peak pressures for two reasons. (See reference 5 for a full discussion.) First, the relative impedance to flow of an airway-lung unit depends on the resistance of the airway, the frequency of ventilation and the compliance of the lung unit (5). Because the BPF has essentially infinite compliance, in the absence of airway impedence, flow would go entirely to the BPF rather than to alveoli. Higher frequencies increase the airway impedance, making it a relatively more important determinant of distribution of airflow and decreasing the importance of compliance. Thus with normal lungs, a marked redistribution of flow can occur as frequencies are increased since airway impedance becomes relatively more significant and compliance less so.

In our patients, unlike models of BPF, the lungs had significant injury and consequent low compliance in addition to the BPF. This decreased the relative importance to total impedance of increasing the frequency and resulted in less redirection of flow away from the fistula.

The second reason a decrease in peak pressures will decrease leakage is that lower pressure leads to less stretch on a tear. Since the area of such a tear will be proportional to the square of its radius, high peak pressures may result in larger leaks (5). In all but one of our patients, the air leak was located peripherally, where changes in pressure are minimized by the intervening resistances. This will decrease the effects of high peak pressures in enlarging the tear and increasing flows.

In some but not all of our patients, flow through the BPF actually increased (Tables 1 and 2). Conceivably, tracheal pressures during HFJV may not have accurately represented alveolar pressures, explaining the increased leak at comparable mean tracheal pressures (10).

High-frequency jet ventilation has been shown to be a safe and effective way of supporting patients with acute respiratory failure (11). Experimental and clinical evidence support its utility in ventilating patients with large airway fistulas (1–3,7). However, based on our study, we feel it must be used selectively in patients with BPF. This reflects the experience of Albelda et al. (12), who noted variable response of leak flow to HFJV.

In our patients, who had parenchymal lung injury as well as a BPF, adequate gas exchange could not be achieved at comparable mean airway pressures with HFJV, although peak airway pressures decreased. While most of the patients could undoubtedly have been supported with HFJV had we increased the driving pressure or the inspiratory time, this would presumably have been at the cost of increased leak. We suggest that the use of HFJV for long-term support of the patient with BPF should include careful measurement of airway pressures, blood gas tensions, and leaked volumes to determine if desired goals are being achieved. Special caution should be used in the face of substantial concurrent parenchymal lung disease.

We acknowledge the technical assistance of the respiratory therapists of the Harborview Medical Center.

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Effect of Spontaneous Sighs on Arterial Oxygenation during Isoflurane Anesthesia in Humans

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GRIM PS, FREUND PR, CHENEY FW. Effect of spontaneous sigh on arterial oxygenation during isoflurane anesthesia in man. Anesth Analg 1987;66: 839–42.

The presence, frequency, and volume of spontaneous sighs was evaluated in 21 (ASA 1–2) supine patients aged 44 ± 15.2 (SD) yr, during isoflurane–nitrous oxide anesthesia. Before induction the inspiratory capacity of each patient was determined. After induction of anesthesia and tracheal intubation patients breathed spontaneously except for three manual inflations to each patient's predetermined inspiratory capacity at the beginning and end of surgery. Arterial blood gas tensions were measured before and 5 min after each set of mechanical deep breaths and each hour during surgery, the mean duration of which was 2 ± 0.09 hr. Spontaneous sighs occurred in 13 of 21 patients. The average frequency was 6 ± 4 sighs/hr. At $FI_{O_2} = 0.5$, nonsighing patients had an initial PaO_2 of 229 ± 59 mm Hg and sighers had an initial PaO_2 of 162 ± 57 mm Hg ($P < 0.05$). Arterial oxygen did not change in sighing patients during the course of surgery, while in nonsighing patients the PaO_2 decreased from the initial value of 229 ± 60 mm Hg to 170 ± 63 mm Hg ($P < 0.05$). Mechanical deep breaths administered at the end of surgery produced no improvement in oxygenation in either sighers or nonsighers. The presence or absence of sighs did not correlate with PaO_2 or $PaCO_2$. Though the results suggest that spontaneous sighs in some patients may function to help maintain arterial oxygenation, all patients maintained their PaO_2 while breathing spontaneously under general anesthesia in the supine position.

Key Words: VENTILATION—sighs. ANESTHETICS, VOLATILE—isoflurane.

Periodic spontaneous deep breaths occur in many mammalian species including man (1). The increase in lung compliance and decrease in the work of breathing associated with sighs suggest that they serve to maintain pulmonary function by preventing or transiently reversing atelectasis (2,3). However, clinical data from mechanically ventilated human subjects have shown no significant improvement in oxygenation between those who were given and those not given sighs (4). However, mechanically administered deep breaths may produce a ventilatory pattern less efficient than a spontaneous sigh (4,5).

Frequency of spontaneous sighs in anesthetized humans and the effectiveness of these sighs in maintaining oxygenation have not been determined. Sighs may be one of the mechanisms by which patients breathing spontaneously under general anesthesia maintain oxygenation and alveolar stability (6,7). This study was designed to evaluate both the frequency and volume of the spontaneous sigh and the effect (the mechanical and spontaneous sigh on gas e change in patients in the supine position during ge eral anesthesia with nitrous oxide–isoflurane.

Methods

Twenty-one (ASA 1–2) patients (3 women and 18 mer aged 44 ± 15 yr and scheduled for nonthoracic ar nonabdominal surgery, were studied. The majori (15 of 21) had orthopedic surgery and the rest unde went head and neck surgery. Five (all men) had smoking history (average, 14 pack-years) but no hi tory of a chronic productive cough.

After institutionally approved, informed conse was obtained, patients were premedicated with 5– mg IV diazepam. Inspiratory capacity was measure using a Bournes LS-50 Spirometer. A radial arte catheter was inserted and anesthesia was induced wi 4–5 mg/kg thiopental. Tracheal intubation was fac itated by 1 mg pancuronium followed by 1.5 mg/k succinycholine. Anesthesia was maintained with 50 nitrous oxide–oxygen and an end-tidal concentratic of isoflurane measured by mass spectrometry (SAR that provided cardiovascular stability, patient in

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Table 1. Subject Characteristics, Arterial Blood Gas Data, and Sigh Volume and Frequency

	Mean ± SD for sighers	Mean ± SD for nonsighers	Mean ± SD for both groups
Age (yr)	48 ± 14[a]	38 ± 15	44 ± 15
Weight (kg)	77 ± 10	74 ± 10	80 ± 11
Smoking history (pack-years)	14 ± 5[b]	14 ± 5[c]	14 ± 5
Inspiratory capacity (ml)	3331 ± 1039	3355 ± 846	3343 ± 993
Length of surgery (hr)	2 ± 0.8	2 ± 1	2 ± 0.9
Tidal volume (ml)	221 ± 43	245 ± 40	230 ± 53
Initial Pa_{O_2} (mm Hg)	162 ± 57[a]	229 ± 59	187 ± 66
Final Pa_{O_2} (mm Hg)	165 ± 46	170 ± 62	167 ± 52[d]
Average Pa_{O_2} (mm Hg)	161 ± 47[a]	191 ± 3	173 ± 50
Change in Pa_{O_2} after deep breath (mm Hg)	1 ± 44	23 ± 64	9 ± 51
Sigh volume (ml)	552 ± 158	—	—
Sigh frequency (sighs/hr)	6 ± 5	—	—

[a] $P < 0.05$ between sighers and nonsighers.
[b] $n = 3$.
[c] $n = 2$.
[d] $P < 0.05$ compared to the preceding value.

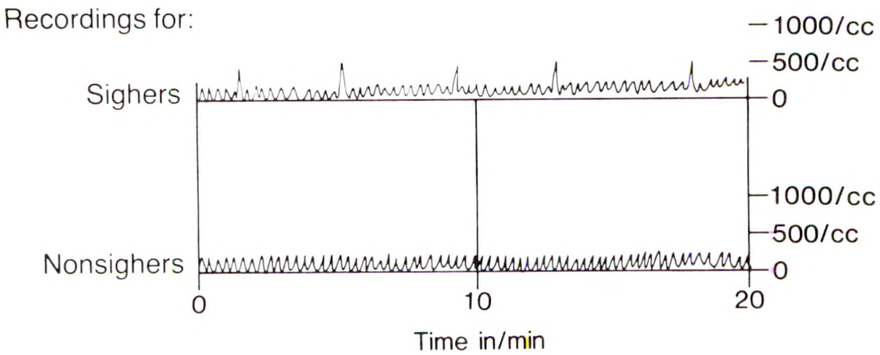

Figure 1. Representative 20-min segments of tidal volume records from sighing and nonsighing patients (chart recorder speed 0.7 cm/min).

mobility, and spontaneous ventilation. No narcotics were given.

A breath-by-breath recording of tidal volume was made throughout the operation using the Bournes LS-50 Spirometer inserted in the inspiratory side of the breathing circuit and connected to a chart recorder. The recorder was calibrated before each study by means of a 1-L syringe. Tidal volume and sigh volume were measured from the chart record.

When spontaneous respiration returned after induction, the lungs were manually hyperinflated to three times their preanesthesia inspiratory capacity. This was repeated at the end of surgery. Otherwise the patients were allowed to breath spontaneously throughout surgery. Arterial blood gas tensions were measured immediately before and 5 min after each hyperinflation and at 1-hr intervals during surgery using a Radiometer (Copenhagen) blood gas machine. A sigh was defined as a single spontaneous breath with a tidal volume at least 50% greater than the average tidal volumes in the preceding and following minute.

Recorded sigh activity was confirmed by the change in breath sounds, which were monitored continuously by the anesthetist. The predetermined criteria for terminating a study included: failure to achieve adequate surgical anesthesia with spontaneous ventilation; $Pa_{CO_2} > 55$ mm Hg; frequent premature ventricular contraction (PVC); and failure to maintain $Pa_{O_2} \geq 100$ mm Hg. Data were analyzed by Student's paired and unpaired *t*-test. Results are expressed as mean ± SD.

Results

Thirteen of the 21 patients spontaneously sighed during the course of anesthesia, which lasted 1–3 hr with a mean of 2.1 ± 0.9 hr. (See Table 1.) No study was terminated because of inadequate anesthesia, elevated Pa_{CO_2}, cardiovascular instability, or a low Pa_{O_2}. Representative 20-min segments of chart recordings for sighers and nonsighers are shown in Figure 1. Comparison of population characteristics (Table 1) between the two groups showed no statistically signif-

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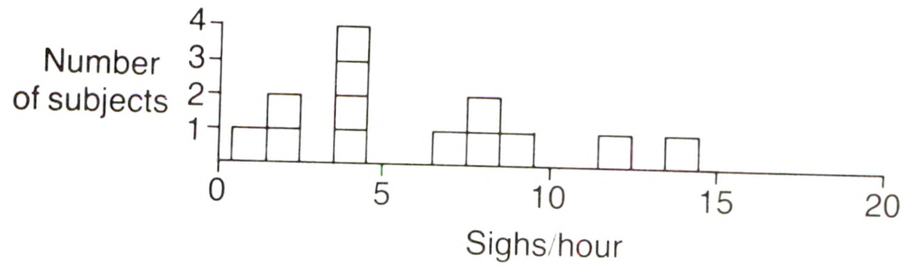

Figure 2. Distribution of sighing patients according to sigh frequency.

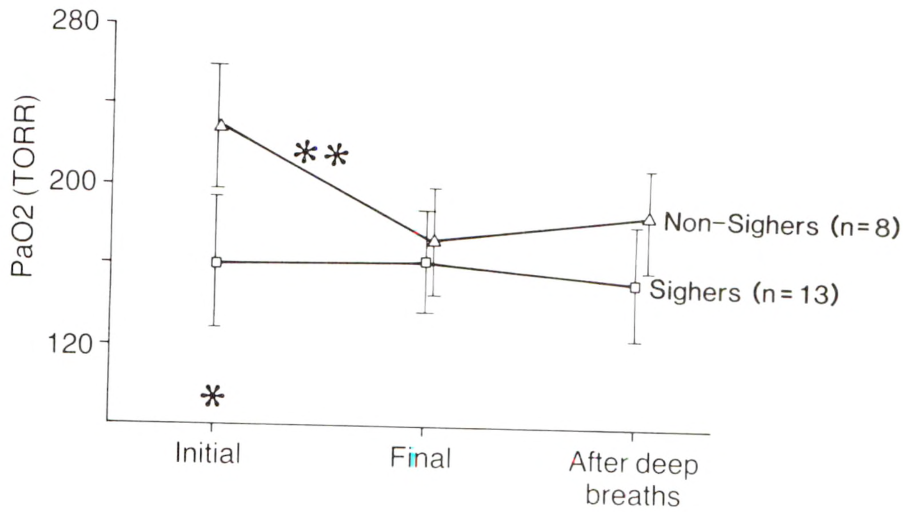

Figure 3. Pa_{O_2} in sighers and nonsighers during surgery and after final mechanical hyperinflation. *The initial Pa_{O_2} of both groups are significantly different at $P < 0.05$. **The difference between the initial and final Pa_{O_2} in nonsighers was statistically significant ($P < 0.05$). There were no other statistically significant intergroup or intragroup differences.

icant difference in weight, average tidal volume, or duration of surgery. Sighing patients were an average of 10 yr older than nonsighing patients. Smoking history was similar in both groups. When sighing occurred, it was present throughout anesthesia at an average frequency of 6 ± 4 sighs/hr with a range of 1–14 sighs/hr (Fig. 2). Sighs averaged 522 ± 158 ml, 2.4 times the size of the average tidal volume and 0.15 times the size of the inspiratory capacity. In some individuals the pattern of sighing showed a marked periodicity. Patients who did not sigh at the beginning of surgery did not sigh even though oxygenation decreased from an initial mean Pa_{O_2} of 229 ± 59 to 176 ± 55 mm Hg during the first 2 hr.

Blood gas tensions differed between the two groups (Fig. 3). At the start of anesthesia nonsighers had significantly higher initial Pa_{O_2} (229 ± 59 mm Hg) levels than sighers (Pa_{O_2}, 162 ± 57 mm Hg). During surgery the Pa_{O_2} in nonsighers decreased to 170 ± 63 mm Hg, a level significantly lower than their initial Pa_{O_2} (229 ± 59 mm Hg) and approximately the same as the final Pa_{O_2} of 165 ± 46 in the sighing group. Sighers showed no significant change in Pa_{O_2} during the course of anesthesia. Mechanical hyperinflation at the end of the procedure produced no change in Pa_{O_2} in either sighers or nonsighers. Both groups had a similar mean Pa_{O_2}, the levels of which remained constant during surgery. Mean Pa_{CO_2} levels in both groups during surgery were similar (sighers Pa_{CO_2}, 42 ± 9 mm Hg; nonsighers Pa_{CO_2}, 43 ± 7 mm Hg). In the sighing group there was no correlation between sigh volume, sigh frequency, Pa_{CO_2} or Pa_{O_2}.

Discussion

The sighing observed in 13 of the 21 patients demonstrates that spontaneous deep breaths do occur in some patients during isoflurane anesthesia. Both sighing and nonsighing patients maintained adequate levels of oxygenation and no study had to be terminated because of $Pa_{O_2} < 100$ mm Hg, $Pa_{CO_2} \geq 55$ mm Hg, or PVC despite anesthesia for up to 3 hr.

It was not apparent why some patients sighed and others did not, although initial Pa_{O_2} values differed significantly between the two groups. Nonsighers had significantly higher initial Pa_{O_2} levels than sighers and these values declined significantly during the course of surgery so that the final Pa_{O_2} values approximated that of sighers. Sighers, although beginning with a lower Pa_{O_2}, showed no comparable decline in Pa_{O_2}. The initial difference in Pa_{O_2} between the groups and the subsequent decline in Pa_{O_2} in the nonsighers

seemed physiologically insignificant. It also seems unlikely that the mean 10-yr difference in age could explain the difference between the two groups. The relative stability of oxygenation seen in sighers during the course of anesthesia suggests that spontaneous sighs may serve to stabilize oxygenation under conditions where impaired oxygenation may occur.

Previous studies have shown no benefit from manual hyperinflation in anesthetized (8) or sedated, mechanically ventilated humans (4). Unanesthetized subjects were mechanically ventilated with higher tidal volumes than would occur with spontaneous ventilation (4), or, if subjects were allowed to breath spontaneously, the study did not control for the presence of spontaneous sighs (8). These conditions may have obscured any benefit from mechanical hyperinflation. In the present study, these factors were controlled, but manual hyperinflation at the end of surgery did not significantly alter the arterial PaO_2 in either sighers or nonsighers. Because we measured PaO_2 5 min after hyperinflation and cannot rule out immediate or transient increase in PaO_2 due to hyperinflation, any increase would have been of brief duration.

The apparent paradox of the effectiveness of spontaneous sighs and the ineffectiveness of mechanically administered sighs has been attributed to the difference in ventilatory patterns between the two types of deep breaths (9). In awake subjects, Bynam et al. found spontaneous deep breaths to be more effective than positive pressure ventilation in diminishing the ventilation–perfusion mismatch that occurred in the supine position (10). Sighs have been characterized as a respiratory reflex mediated by the vagus that is regulated by afferent information from peripheral chemoreceptors (11–13). In our patients, however, there was no correlation between sigh frequency or volume of sigh, PaO_2, or $PaCO_2$.

Many of the sighing patients showed a rhythm to their sighing. A similar pattern has been previously reported by McCutcheon who observed "the predictable recurrence in regular sequence of deep breaths" in a variety of mammals, including man (14). The duration of these cycles was positively correlated with body size (14). In man deep breaths occurred periodically at a rate of three per hour (14). Shorter oscillations in respiratory amplitude, lasting approximately 25 sec, can occur in association with changes in cardiac output (15). These cyclical breathing patterns have been said to be a function of variation of neuronal activity due to a central nervous system pacemaker. In our patients cycle length varied markedly among sighing individuals but averaged approximately 6 sighs/hr and remained stable during the course of anesthesia. The rhythms seen in some patients and the lack of correlation between a patient's sigh frequency, the PaO_2 or $PaCO_2$, or smoking history suggests that, under certain circumstances, a central rather than peripheral stimulus initiates sighs. During these conditions, central pacemaker activity may control their frequency. This may explain the persistence of sighs in laboratory animals who have undergone a vagotomy (11).

In conclusion, our results show that neither spontaneous nor mechanical sighing is necessary for adequate oxygenation during isoflurane anesthesia in the supine position. Our results also suggest that spontaneous sighs in some patients may function to help maintain arterial oxygenation. It is not clear from our data why some patients sigh and others do not and whether this effect is unique to isoflurane.

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Influence of Age on Vascular Absorption of Lidocaine from the Epidural Space

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FINUCANE BT, HAMMONDS WD, WELCH MB. Influence of age on vascular absorption of lidocaine from the epidural space. Anesth Analg 1987;66:843–6.

The purposes of this study were to evaluate the effect of age on the vascular absorption of local anesthetics during epidural anesthesia and to corroborate the clinical observations of other investigators with respect to age. Using the arbitrary definition of significance ($P < 0.05$), the maximum serum levels of lidocaine (C_smax) did not differ significantly with age, however, P values were equal to 0.06. Furthermore, the time to C_smax was significantly faster in elderly patients ($P < 0.00001$). In conclusion, the mass of local anesthetic solution should be reduced in elderly patients undergoing epidural anesthesia because there is a greater segmental spread, and serum levels of local anesthetics are increased.

Key Words: ANESTHETIC TECHNIQUES—epidural. AGE—epidural anesthesia. PHARMACOKINETICS—epidural lidocaine.

Bromage (1) demonstrated that the mass of local anesthetic drug required to achieve a given segmental level of epidural anesthesia was reduced in elderly patients. He reasoned that with age, the intervertebral foramina became progressively occluded with connective tissue. Consequently, local anesthetic solutions injected epidurally might have a greater longitudinal spread. On the other hand, in younger individuals, the patency of intervertebral foramina allowed lateral escape of local anesthetic solutions injected epidurally. This increased longitudinal spread might lead to an increased area for absorption and, consequently, one might expect higher peak serum levels of local anesthetic drugs in elderly patients. Tucker and Mather (2), on the other hand, have argued that because of the decreased cardiac output and vascular perfusion that accompanies aging, absorption from the epidural space might be slower in elderly patients. Therefore, the elderly should have lower serum levels of local anesthetics and be at less risk from local anesthetic toxicity.

With this controversy in mind, we compared the maximum serum lidocaine levels (C_smax) occurring in two groups of male patients (young and elderly) after epidural injection of local anesthetic. In addition, we set out to corroborate previously reported clinical findings pertaining to old age during epidural anesthesia.

Materials and Methods

This study was approved by the Human Investigations Committee of Emory University. Written informed consent was obtained from each patient after a detailed explanation of the protocol. Thirty-six men (ASA Class I–III) scheduled for elective surgery were divided equally into two groups on the basis of age: those 30 yr or younger in one group, and those 60 yr or older in the other.

At the start of the procedure each patient received 500 ml of D_5LR through a peripheral intravenous catheter. An 18-gauge plastic cannula was inserted, for sampling purposes, into the right internal jugular vein and connected to a heparinized extension tube with a three-way stopcock.

Epidural anesthesia was performed with the patient in the sitting position. A skin wheal was raised over the L3–4 interspace, using bupivacaine 0.25%, after which an 18-gauge Hustead needle was inserted into the epidural space using the loss of resistance to air injection technique. On entering the epidural space, the bevel of the needle was pointed cephalad and 2% lidocaine without epinephrine (4 mg/kg) was injected

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Table 1. Surgical Procedures

Procedure	Age: Young	Old
Hernia Repair	8	4
Urologic	2	13
Anal/rectal	3	1
Orthopedic	5	—

over 60 sec. Signs and symptoms of toxicity, including progressive drowsiness, numbness of the tongue and lips, speech disturbance, and dizziness, were sought during the injection. A catheter was then advanced about 3 cm into the epidural space for supplementation at a later time. The patient was then placed in the supine position, and blood pressure, pulse, and respiration were recorded at 5-min intervals using standard equipment.

The time from completion of injection until loss of pin-prick sensation to T-12 was recorded. In addition, the time until maximum sensory block was achieved, and the maximum number of dermatomes blocked were recorded. To facilitate calculations, and because of occasional uneven blocks, each dermatome was divided into two segments separated by the median plane. The time between injection and two-segment regression of the level of anesthesia was also recorded. Concurrently, motor blockade was assessed using Bromage's four point scoring system (3). Ability to flex the knees and feet was scored 0; just able to move the knees, 1; able to move the feet only, 2; and unable to move the feet or knees, 3.

Blood samples were drawn from the internal jugular cannula 1, 5, 10, 20, 40, 80, 120, and 240 min after epidural injection of the 4 mg/kg lidocaine. In eight young patients, additional samples were drawn at 15 min. Venous serum lidocaine concentrations were measured by enzyme immunoassay (EMIT) technique. The EMIT technique for lidocaine assay has proven to be accurate with a high degree of specificity and precision (4).

Based on the characteristics of the data, either a two-sample t-test, a Mann-Whitney U-test, a χ^2-test, or Fishers exact test was used to determine whether the two groups differed significantly. Statistical significance was assumed at $P < 0.05$.

Results

There was some diversity between the two groups with regard to the surgical procedures performed (Table 1). Weight and height did not differ significantly between the two groups, but the $C_s$max was increased by about 20% in elderly patients ($P = 0.06$) (Table 2). However, the time from injection until $C_s$max was significantly reduced ($P < 0.00001$) in elderly patients (Table 3). The majority of older patients had reached $C_s$max within 10 min, whereas the younger patients were more likely to reach their highest level after 10 min.

Table 2. Patient Characteristics and Peak Serum Lidocaine Levels ($C_s$max)

	Older men (n = 18)	Younger men (n = 18)	$P <$ t-test
Age in yr (range)	68.9 ± 6.4 (61–82)	25.3 ± 3.3 (19–30)	—
Weight in kg (range)	74.1 ± 11.1 (49–92)	71.8 ± 7.7 (59–86)	NS
Height in cm (range)	175.4 ± 7.3 (162.5–188.8)	178.0 ± 6.1 (169–188)	NS
$C_s$max expressed as mg/ml (range)	3.29 ± 1.34 (1.6–6.0)	2.73 ± 0.68 (1.9–4.5)	$P = 0.06$

Values expressed as mean ± SD.
NS no statistically significant difference.

Table 3. 2 × 2 Contingency Table—Time to Peak Serum Lidocaine Level

	Number of Subjects: ≤10[a]	>10[a]	Total
Younger men	1[b]	17	18
Older men	14	4	18
Total	15	21	36

[a]Time in minutes to C_s Max of Lidocaine.
[b]Fishers exact; $P < 0.00001$.

In addition, older patients had a significantly greater maximum sensory segmental spread (Table 4). However, as shown in Table 5, there was no significant difference between the two groups in the onset of sensory analgesia. Nor was there a significant difference in the time until maximum sensory blockade was reached. The times to two-segment regression and maximum motor score were also similar in the two groups.

With one exception, the vital signs remained stable in all cases. One patient in the older group developed moderate hypotension (systolic blood pressure 80 mm Hg) approximately 1 hr after discharge from the recovery room. This was rapidly corrected with leg elevation, intravenous fluids, and vasopressors. The etiology of the hypotension was uncertain but may have been related to acute bladder distension. There were no long-term sequelae, and the patient was discharged from the hospital 1 week later.

No major technical difficulties were encountered with either the internal jugular cannulation or per-

Table 4. Maximum Segmental Sensory Block

	Older men (n = 18)	Younger men (n = 18)	P < t-test
Number of segments blocked	35.2 ± 5.65[a]	29.5 ± 7.63	<0.05
(range)	(26–44)	(16–44)	

Values expressed as mean ± SD.
[a]Mann-Whitney U = 88.50; P = 0.0196.

Table 5. 2 × 2 Contingency Table—Time to Loss of Pin Prick Sensation at T_{12} (χ^2 Analysis)

	Number of subjects		
	≤7.5[a]	>7.5[a]	Total
Older men	8[b]	10	18
Younger men	12	6	18

[a]Time in minutes to pin prick sensation.
[b]χ^2 = 1.80; P = 0.1797.

formance of the epidural anesthesia. There were no dural taps, and blood was not observed in the epidural needle or catheter of any patient. There were no signs or symptoms of toxicity.

Discussion

Clinical pharmacologists have demonstrated that age is associated with altered responses to many drugs. Because of the age-related changes in cardiac, hepatic, and renal function, the elderly would seem to be at increased risk of developing toxic levels of many types of drugs, even after routine clinical doses.

In most clinical studies, an event is considered significant if the probability of that event, occurring by chance, is less than one in 20 ($P < 0.05$). In this study, the $C_s$max did not differ significantly with age, using that arbitrary definition. In fact, the P value was equal to 0.06. Furthermore, it is highly probable that the P value for $C_s$max would meet the arbitrary definition of significance if the sample size was increased. Therefore the very least one can say is that there was a strong tendency towards increased peak serum levels of lidocaine in the elderly group.

Braid and Scott (5) also attempted to establish a relationship between $C_s$max and age, and found only a very weak correlation. In that study, only three of their 26 patients were older than 60 yr, and the study was conducted solely in women. Bromage suggests that the decreased epidural dose requirement in the elderly is due, in part, to anatomic changes in the epidural space, with progressive occlusion of the intervertebral foramina and, consequently, increased spread of local anesthetic in the epidural space. If this is true, it appears likely that the area for absorption would be increased and would result in higher serum levels.

A progressive decline in cardiac output with increasing age (6) might offset the tendency for the increased absorption of lidocaine from the epidural space. Mather et al. (7) have demonstrated a direct relationship between cardiac output and the absorption of local anesthetic drugs from the epidural space.

A number of other factors play a role in the distribution and elimination of local anesthetic drugs. These include the volume of distribution, protein binding, and the rate of excretion of these drugs. These parameters were not evaluated in this study; however, based on current knowledge of pharmacokinetics in the elderly (8), it is likely that the volume of distribution, degree of protein binding, and ability to eliminate local anesthetic drugs would be reduced, all of which would tend to raise serum levels of local anesthetics. It should be noted that there was considerable diversity between the two groups in terms of the surgical procedure performed. The majority of patients in the elderly group were treated for urologic problems, whereas those in the younger age group required hernia repairs. This difference should not have influenced the vascular uptake of local anesthetic drugs from the epidural space, because the important earlier measurements were taken before surgery commenced and before any major fluid shifts had taken place.

It was also interesting to note that the time required to achieve $C_s$max was significantly shorter in elderly patients. One might speculate that this could be a hydrostatic effect. Usubiaga et al. (9) have shown that the residual hydrostatic pressure in the epidural space after injection, increases directly in proportion to age. Furthermore Kirk and Laursen (10) have demonstrated a tendency in human aortic membrane toward increased permeability of the connective tissue with age. If this applies to connective tissue in the epidural space, more rapid diffusion and thus earlier peak serum levels might result. Another explanation might be that the difference in time to peak serum concentrations is methodologic. In this study, the sampling interval was 1, 5, 10, 20, 40, 80, 120, and 240 min. The time to reach $C_s$max was significantly faster in elderly patients at 10 min, compared to 20 min for younger patients. When these data were analyzed using Fishers exact test, P values were less than 0.00001. Would the results have been different if we had sampled at 15 min? We tried to resolve this problem by sampling eight patients in the younger age group at 15 min. The $C_s$max occurred at 15 min in two out of eight patients.

If connective tissue is more permeable in the elderly, one might also expect a progressive decrease in the onset of motor and sensory anesthesia with age. This was not true in our study. Our failure to detect a difference in the latency may have resulted from sensory testing that was too infrequent. Bromage (11), however, tested skin analgesia at 1-min intervals, after epidural injection of lidocaine, but was unable to detect any significant correlation between age and latency in either normal or arteriosclerotic patients. He proposed then that the increased permeability of connective tissues in the elderly might be partly offset by hypertrophy of that tissue around the nerve fiber.

In none of our patients did we see evidence of toxicity. This is in agreement with the relatively low incidence of toxic manifestations reported by others during epidural anesthesia (12). In contrast, Lie et al. (13), in an evaluation of IV lidocaine for the prevention of ventricular fibrillation, observed a relatively high incidence of side effects (15%). In addition, side effects were more common in patients aged 60 yr or older than in younger patients. These side effects developed at serum lidocaine levels ranging from 2.9 to 6.9 μg/ml. Perhaps the paucity of side effects noted in our elderly group of patients, even at blood levels greater than 5 μg/ml, can be explained by a failure to achieve a steady state. As Scott (14) has suggested, lidocaine levels in the absence of a steady state correlate poorly with symptoms of toxicity.

During the last several years, Bromage's observations pertaining to age and epidural dose requirement have been challenged (15). In this study, we verified that the dose per segment required to achieve a given level of epidural anesthesia is reduced in elderly patients. In addition to this, we have shown that $C_s$max of local anesthetic drugs is higher and the time to $C_s$max is shorter in elderly patients. On clinical grounds alone, it is clear that the dose of local anesthetic drug should be reduced in elderly patients undergoing epidural anesthesia. There may also be pharmacokinetic reasons why the dose of local anesthetic drugs should be reduced.

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Pupillary Diameter and Ventilatory CO_2 Sensitivity after Epidural Morphine and Buprenorphine in Volunteers

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RAVNBORG M, JENSEN FM, JENSEN N-H, HOLK IK. Pupillary diameter and ventilatory CO_2 sensitivity after epidural morphine and buprenorphine in volunteers. Anesth Analg 1987;66:847–51.

The aim of this study was to correlate pupillary diameter with respiratory depression for 20 hr after epidural administration of morphine or buprenorphine. Pupillary diameter and the ventilatory sensitivity to CO_2 were measured in six healthy volunteers at various times (0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 20 hr) in two sessions, separated by at least 1 week, at which either epidural morphine, 4 mg, or epidural buprenorphine, 0.15 mg, was administered randomly in a double-blind manner. Three of the six volunteers received 0.3 mg buprenorphine epidurally in a third session. Pupillary diameter was measured with a modified Essilor pupillometer. The ventilatory CO_2 sensitivity was measured by a modified Read rebreathing technique. The ventilatory parameters measured were mouth occlusion pressure during the first 0.1 sec of inspiration ($P_{0.1}$), end-tidal CO_2 (PET_{CO_2}), tidal volume (V_T) and respiratory rate (RR). Slopes of the linear regression lines ($P_{0.1}/CO_2$, V_T/CO_2, $\dot{V}_E/CO_2$, and RR/CO_2) and the intercept values of the regression lines and PET_{CO_2} = 7.2 kPa ($P_{0.1}$:7.2, V_T:7.2, $\dot{V}_E$:7.2, and RR: 7.2) were calculated. Pupillary diameter after epidural morphine was smallest at the second hour and had returned to normal after eight hours. After epidural buprenorphine there were two periods of miosis, one at 1–3 hr, the other at 10 hr. With epidural morphine, a statistically significant correlation ($P < 0.05$) was found between pupillary diameter and $\dot{V}_E/CO_2$, $\dot{V}_E$:7.2, $P_{0.1}$:7.2, and V_T:7.2. With epidural buprenorphine 0.15 mg a significant correlation was found between pupillary diameter and $\dot{V}_E$:7.2 and $P_{0.1}$:7.2. With epidural buprenorphine 0.3 mg the correlations between pupillary diameter and $\dot{V}_E$:CO_2, $\dot{V}_E$:7.2, and $P_{0.1}$:7.2 were significant. The results indicate that the neural control of respiration and of pupillary diameter is influenced synchronously by epidural opioids and that the pupillary response may serve as an indicator of respiratory depression.

Key Words: ANALGESICS—morphine, buprenorphine. ANESTHETIC TECHNIQUES, EPIDURAL—narcotics. EYE—pupil.

The dose-dependent pupillary constriction produced in humans by opioids is easily observed and quantified. The possibility of correlation between miosis and respiratory depression during analgesic therapy with opioids has not been evaluated. With the introduction of epidural opioid administration, the necessity to monitor respiration has been accentuated because of late respiratory depression. Several reports on life-threatening late respiratory depression (1,2) have restricted the use of epidural opioid administration in pain treatment.

The aim of this study was to measure changes in pupillary diameter after epidural administration of morphine and buprenorphine and to correlate the changes in pupillary diameter with the changes in ventilatory CO_2 sensitivity to determine whether pupillary size might be a reliable index of respiratory depression associated with epidural narcotics.

Method

The study was approved by the Copenhagen County Ethical Committee and all subjects gave informed consent. The study followed a double-blind, randomized, and paired design. Six healthy male volunteers aged 29–36 yr participated at two sessions separated by at least 1 week. Each subject was observed in the ICU for 24 hr at each session. Each session involved only one observer. An epidural catheter was inserted at L3–L4. Epidural placement was validated by test doses of lidocaine 1%, 3 ml, to rule out spinal placement followed by 5 ml to assure that segmental analgesia

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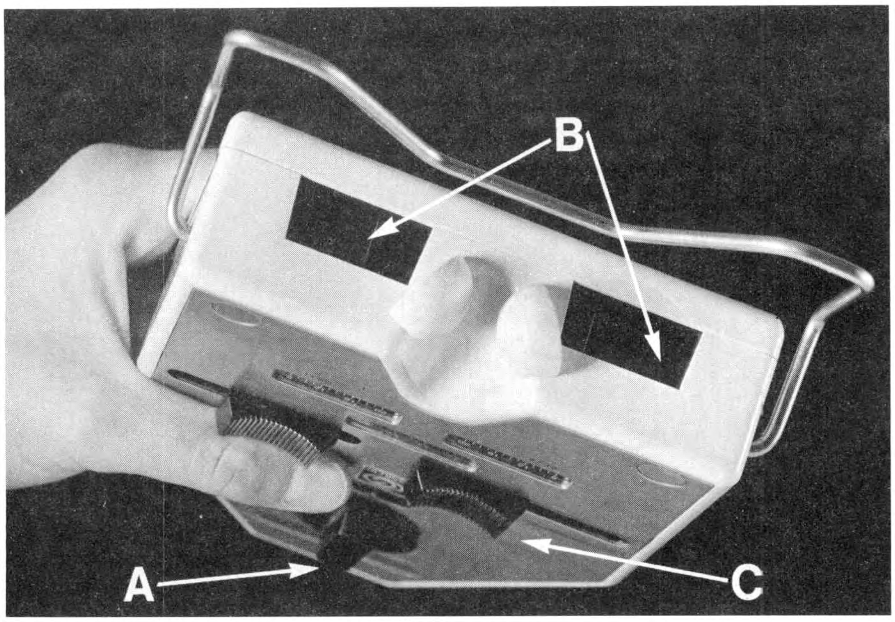

Figure 1. The Essilor pupillometer used in the study. **A**—Eye of the observer. **B**—Eyes of the subject. **C**—Slides and scale.

could be achieved. Using coded syringes prepared by a physician not associated with the study, 4 mg preservative-free morphine chloride in 10 ml isotonic saline was injected on one occasion and 0.15 mg preservative-free buprenorphine in 10 ml isotonic saline on the other. The administration of 0.3 mg buprenorphine in three subjects was not blinded.

Pupillometry followed by CO_2 response curve recording was performed before and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 20 hr after injection. Subjects were not allowed to take coffee or to smoke for 6 hr before or during the study.

Pupillometry was performed before each ventilatory sensitivity test with a modified Essilor pupillometer (Essilor, France) originally constructed to measure the distance between the pupils (Fig. 1). The pupillometer provides a constant, weak illumination of the eyes (400 candela/m^2) and parallel eye axes, thus avoiding pupillary constriction due to convection. Two vertical wires were moved individually in the frontal plane by two slides to the medial and lateral rims of the left pupil. Objects are twice natural size. The diameter of the pupil is read on a scale divided by 0.2-mm markers. The pupillometer was applied to the face of the volunteer for 30 sec before each measurement to allow adaptation of the retina to the illumination in the box. The pupillary diameter changes cyclically (hippus), and in this study we chose the maximal diameter during a 10-sec observation period. Pupillometry was repeated four times at each line of measurement and the median calculated.

Ventilatory sensitivity to CO_2 was determined by a modification of the Read rebreathing technique (3). Subjects breathed a mixture of 6% CO_2, 50% O_2 and 44% N_2 in a closed circuit containing 10 L of the gas mixture and allowing the inspired CO_2 concentration to increase to 9–10%. Gas was continuously sampled at the lips at a rate of 0.5 L/min, with CO_2 being measured with an infrared analyzer (Capnograph, Godart) and recorded on a paper recorder (Godart). Occlusion pressure, the negative pressure generated during inspiration against a closed inspiratory valve in the first 0.1 sec ($P_{0.1}$) was measured using a modified method described by Whitelaw et al. (4). The inspiratory pressure triggering measurement was -2 cm water. The modification allowed several measurements to be made during each CO_2 stimulation without the subject's knowledge. $P_{0.1}$ was recorded simultaneously with CO_2 concentration. At least 15 $P_{0.1}$ recordings were made at each point in the study. Tidal volumes (V_T) were recorded with a fluidistor (AGA U.S. 800). Respiratory rate (RR) was measured from the $P_{0.1}$ tracing, and minute ventilation ($\dot{V}_E$) was calculated from RR and V_T.

Statistical significance of changes in the pupillary diameters was evaluated with the Friedman test. When comparing pupillary diameter at different times, the Mann-Whitney rank sum test was used. Wilcoxon's test for pair differences was used to compare the pupillary responses to the two drugs. The correlations between the respiratory parameters (medians) and the pupillary diameter (medians) were tested by Spearman's rho (5). The value $P < 0.05$ was accepted as indicating statistical significance.

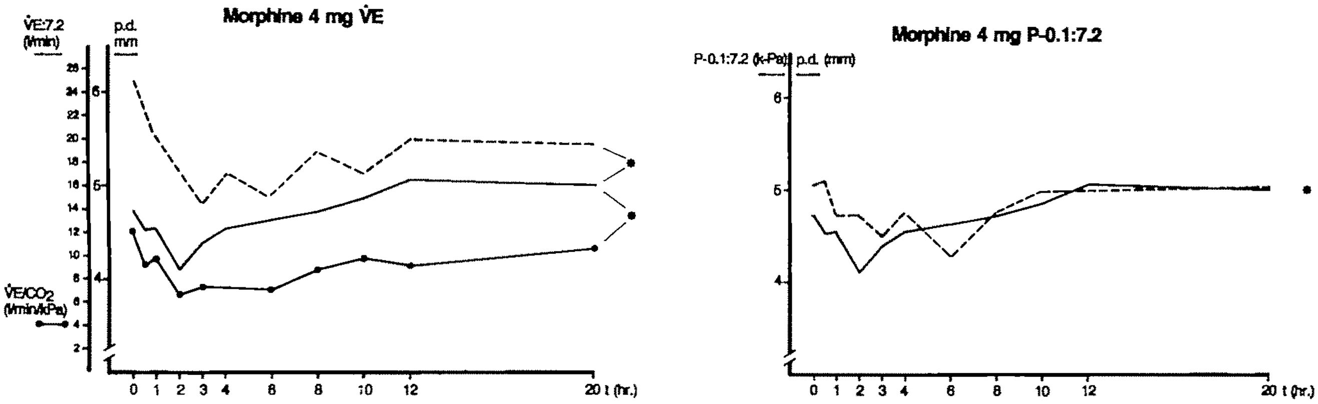

Figure 2. Time-response curves after epidural morphine, 4 mg. Left, Pupillary diameter (—), V̇E:7.2 (—), and V̇E/CO_2 (●—●); right, Pupillary diameter (—) and $P_{0.1}$:7.2 (—). Asterisks indicate statistically significant correlation between the curves marked.

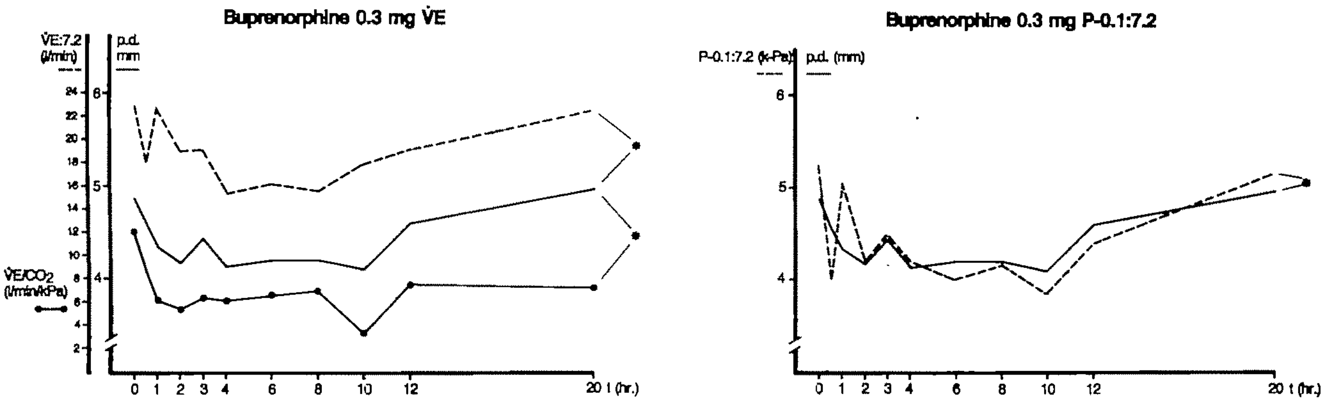

Figure 3. Time-response curves after epidural buprenorphine, 0.3 mg. Left, pupillary diameter (—), V̇E:7.2 (—), and V̇E/CO_2 (●—●); right, Pupillary diameter (—) and $P_{0.1}$:7.2 (—). Asterisk indicates statistically significant correlation between the curves marked.

Results

Slopes of the linear regression lines ($P_{0.1}/CO_2$, VT/CO_2, V̇E/CO_2, and RR/CO_2) and the intercepts between the regression lines and PCO_2ET = 7.2 mm Hg ($P_{0.1}$:7.2, VT:7.2, V̇E:7.2, and RR:7.2) were calculated. Correlation coefficients (r) were statistically significant (r:0.68–0.99) for all regression lines but the RR/PCO_2ET line.

After 4 mg morphine, the miotic response was maximal after 2 hr and returned to normal after 8 hr. No late miosis was observed (Fig. 2). The monophasic course of the pupillary size was statistically significant (Friedman's test). The difference between baseline pupillary diameter and that at t = 2 hr was statistically significant. Statistically significant correlation was found between pupillary diameter and V̇E/CO_2 (ρ = 0.71), V̇E:7.2 (ρ = 0.62), VT:7.2 (ρ = 0.71), and $P_{0.1}$:7.2 (ρ = 0.77) (Figs. 2*A* and 2*B*).

After 0.15 mg buprenorphine, the pupillary response was biphasic with maximal miosis after 1–2 hr and after 8 hr. The biphasic course was statistically significant (Friedman's test). Pupillary diameter returned to normal after 12 hr (Fig. 3). The pupillary size was significantly different from baseline levels 1, 2, 3, and 10 hr after injection of buprenorphine. Statistically significant correlation was found between pupillary diameter and V̇E:7.2 (ρ = 0.62) and $P_{0.1}$:7.2 (ρ = 0.62) (Fig. 4).

After 0.30 mg buprenorphine, the pupillary response was characterized by a miosis from the second to the tenth hours after injection without any biphasic course. Significant correlation was found between pupillary diameter and V̇E:CO_2 (ρ = 0.77), V̇E:7.2 (ρ = 0.62), and $P_{0.1}$:7.2 (ρ = 0.62) (Fig. 3). Both ventilatory and the pupillary responses after 0.15 mg buprenorphine were significantly more pronounced than after 4 mg morphine (Wilcoxon's test for pair differences).

Discussion

Although opioid-induced miosis is an old observation, the receptor sites mediating this response are still obscure. The peripheral control of the pupillary

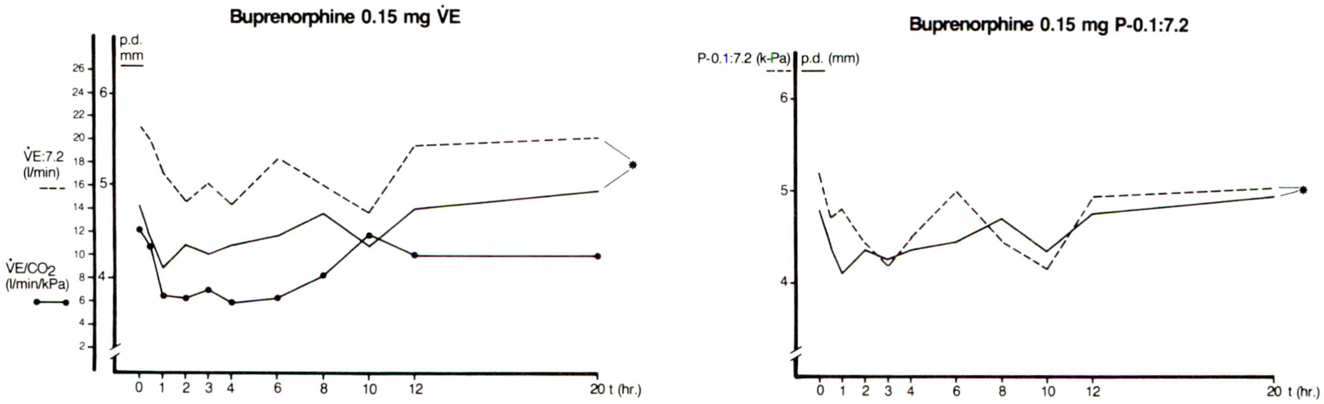

Figure 4. Time–response curves after epidural buprenorphine, 0.15 mg. Left, pupillary diameter (—), $\dot{V}$E:7.2 (---), $\dot{V}$E/CO_2 (●—●); right, pupillary diameter (—), $P_{0.1}$:7.2 (---), and $P_{0.1}/CO_2$ (●—●). Asterisk indicates statistically significant correlation between the curves marked.

by the sympathetically innervated pupillary dilator muscle and the parasympathetically innervated pupillary constrictor muscle is well-described (6,7). Several studies indicate that the latter is the mediator of the opioid miotic action (8,9). In dogs, transsection of the oculomotor nerve abolishes opioid miosis whereas sympathectomy leaves the miotic response unchanged (9). Fear, rage, and acute pain induce mydriasis. Both sympathetic and parasympathetic activity are involved in these actions, but their relative importance is unknown.

Preganglionic parasympathetic fibers in the oculomotor nerve arise in the Edinger–Westphal nucleus, located in the dorsomedial part of the mesencephalon, quite close to the cerebral aquaduct. The activity of neurons in the Edinger–Westphal nucleus is influenced by inputs from higher diencephalic and cortical centers and lower centers in the reticular activating system (9).

Pupillometric studies of the miotic response to opioids in animals indicate that the normal oscillations in the size of the pupil, or hippus, are exaggerated by opioids, and that there exists a strong correlation between the amplitude of the pupillary fluctuations and minute ventilation (6). The existence of hippus thus disqualifies static pupillometric methods. The enhancement of hippus by opioids indicates that both maximal and minimal diameters should be measured when the miotic response to opioids is studied. Fraser et al. (10) studied the miotic effect of opioids (photographic pupillometry; static method) as an index of analgesic effect. No reliable correlation between analgesic effect and miosis was found, and the degree of miosis after an effective dose of an opioid showed considerable interindividual variability. On the other hand, the response in each individual was reproducible and the degree of miosis correlated well with the degree of depression of $\dot{V}$E.

Epidural morphine induces prolonged (11) and biphasic respiratory depression (12,13). The early respiratory depression seen during the first hours after epidural administration appears to be related to the plasma concentration of morphine (14). Late respiratory depression, on the other hand, is thought to be the result of rostral spread of morphine within the CSF (15–17), resulting in high morphine concentration in the CSF surrounding the brain stem and midbrain.

Animal studies (18–20) have demonstrated selective depression of VT without any change in RR, by application of opioids on the ventrolateral medullary chemoreceptor zone and the superficial nuclei in the floor of the fourth ventricle, whereas application on the pontine pneumotaxic center causes reduction of the RR only.

Acute pain enhances respiratory drive (21,22). If the cause of pain is effectively treated—by, for example, epidural local anesthetics in a patient also given morphine systemically—the opioid effect on the respiratory centers may be unopposed, and severe respiratory depression may ensue (21). Both pupillary diameter and respiratory drive thus reflect both pain and emotion, on the one hand, and the effect of opioid, on the other. If pupillary diameter and respiratory drive are influenced synchronously and proportionally by opioids, the degree of miosis may be used as an index of respiratory depression. Although the mouth occlusion pressure may be a sensitive indicator of the respiratory drive, the relevant respiratory parameter of CO_2 elimination is the $\dot{V}$E.

We found a direct relationship between pupillary diameter and both $\dot{V}$E:7.2 and $P_{0.1}$:7.2 in all the three sessions and $\dot{V}$E/CO_2 in two of the three sessions, whereas correlation between pupillary diameter and VT:7.2 was found only after morphine administration.

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The more pronounced ventilatory and pupillary responses after buprenorphine 0.15 mg than after morphine 4 mg indicate that the doses are not equipotent in this respect. The doses used in this study did not induce clinically significant respiratory depression and it is unknown whether the correlation between pupillary diameter and respiratory drive exists during overt respiratory depression. We did not include a placebo in the study and therefore we cannot exclude the possibility that some of the variation in the pupillary size is attributable to physiological fluctuations. On the other hand, we found significant differences in both the response pattern (monophasic after morphine, biphasic after buprenorphine) and the magnitude of the response at the morphine and the buprenorphine sessions. These differences indicate a true pharmacological effect.

A test used in monitoring a vital function such as respiration must have a high sensitivity. This means that if the test is negative (the absence of miosis), the possibility of clinically significant respiratory depression must be negligible. Our study was not designed to evaluate the predictive values of the pupillometry, but the significant covariation of $\dot{V}_E$:7.2 and pupillary diameter is promising and makes studies of the dose–response relationship and the predictive values of pupillometry clinically relevant.

In conclusion, it is possible to demonstrate a statistically significant correlation between pupillary diameter and ventilatory response to CO_2 after epidural administration of morphine and buprenorphine using simple dynamic pupillometric equipment. CNS centers controlling the $\dot{V}_E$ and the pupillary diameter are equally affected by morphine and buprenorphine when these are administered epidurally.

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Activity of Lower Intercostal and Abdominal Muscle after Upper Abdominal Surgery

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DUGGAN J, DRUMMOND GB. Activity of lower intercostal and abdominal muscle after upper abdominal surgery. Anesth Analg 1987;66:852–5.

The decrease in end-expiratory lung volume after upper abdominal surgery has been attributed, in part, to reflex spasm of the abdominal muscles. To examine the influence of abdominal surgery on abdominal muscle tone, electromyographic (EMG) activity of abdominal and lower intercostal muscle was compared before operation with that at 3 hr and at 24 hr after operation in 18 healthy patients undergoing elective gastric or biliary surgery. After operation, EMG activity increased markedly and showed a phasic pattern of activity associated with respiration in most patients. This was characterized by a progressive increase in EMG activity during expiration with an abrupt decrease at the onset of inspiration. We conclude that increased expiratory activity in abdominal and lower intercostal muscle may be responsible for the decrease in lung volumes that occurs after upper abdominal surgery.

Key Words: MEASUREMENT TECHNIQUES—electromyography. MUSCLE—abdominal and lower intercostal. SURGERY, ABDOMINAL—postoperative.

The decrease in end-expiratory lung volume that follows upper abdominal surgery (UAS) (1) has been attributed, in part, to reflex spasm of the abdominal muscles. This has been demonstrated in dogs up to 1 hr after cholecystectomy (2). However, to our knowledge, no information on this is available in humans. This study was designed to investigate the changes in abdominal muscle activity associated with UAS in the first 24 hr after operation.

Patients and Methods

Eighteen healthy patients undergoing elective cholecystectomy ($n = 11$) or gastric surgery (vagotomy, $n = 5$; partial gastrectomy, $n = 2$) through horizontal right upper quadrant or right paramedian incisions were studied. Only patients free from respiratory disease and abdominal pain before surgery were admitted to the study. Patients gave informed verbal consent, and the study was approved by the local hospital ethics committee.

Anesthetic management was standardized. Temazepam, 20 mg, was given by mouth as premedication 2 hr before surgery. Anesthesia was induced with thiopental and maintained with enflurane, 1–2%, and 70% nitrous oxide in oxygen. Tracheal intubation was performed with the aid of succinylcholine. Muscle relaxation was obtained with alcuronium and was reversed with neostigmine at the end of the procedure. Intravenous doses of diamorphine (up to 10 mg) were given in the recovery unit for pain relief, analgesia thereafter being maintained with an IV infusion of morphine sulphate (1 $mg{\cdot}kg^{-1}{\cdot}24\ hr^{-1}$), supplemented if necessary with on-demand morphine by the intramuscular route.

Electromyographic (EMG) signals were simultaneously recorded from three pairs of disposable pregelled silver-silver chloride electrodes with 1-cm pads and placed on the skin surface with their centers 5 cm apart. The skin was prepared with an abrasive jelly and organic solvent. The following positions were used: Lower Intercostal, overlying the 9th right intercostal space in the anterior axillary line; Upper Abdomen, 3 cm below the left costal margin lateral to rectus abdominis; Lower Abdomen, 5 cm below the level of the umbilicus lateral to rectus abdominis on the right. A single reference electrode was placed equidistant from each pair of recording electrodes. The position used for the preoperative recording was marked on the skin, and electrodes were placed in these positions at the end of surgery and before recovery from anesthesia to allow measurements to be made in the immediate postoperative period. Surface electrodes were used to give information about the collective activity of a relatively large portion of muscle, and the placement of the abdominal electrodes

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Table 1. Patient Details

Age (yr)	49.9 ± 17
Weight (kg)	66.8 ± 13
Height (m)	1.67 ± 0.12

Values are mean ± SD.

was chosen to assess the different abdominal muscles. The major contributor to the recorded signals from the upper abdomen would be the external oblique muscle, as the internal oblique muscle in this part of the abdominal wall is tendinous (3). Similarly, the external oblique muscle is tendinous below the umbilicus, so the lower abdominal electrodes would sense activity predominantly from the internal oblique, possibly with some activity from the transversus abdominis below. The EMG signal was amplified (bandwidth 20Hz to 2kHz)(Neurolog NL 104/125) and recorded on FM magnetic tape (Digitimer D146). The signal was subsequently rectified and integrated as an exponential average using a "leaky integrator" (NL 703) with a time constant of 100 msec. Both the direct and integrated signal were recorded with a UV galvanometer recorder (Bell and Howell 5-137). The gain setting of the amplifier was noted at each assessment, and the recordings were calibrated with known calibration voltages fed to the recorder and integrator. The zero base lines for the integrated EMG were recorded after each set of measurements. These zeros were obtained by connecting the skin electrodes together. After integration of the direct signal the larger ECG signal was clearly distinguishable from muscle EMG, and did not interfere with quantitative assessment of muscle activity.

Recordings of muscle activity were made with the patient resting in the supine position over a 15-min period before operation, and at 3 hr and at 24 hr after operation. Before operation, a further 5-min recording was made with the patient standing.

EMG activity is expressed in terms of averaged root mean square voltage of the recorded signal, in microvolts. Because the size of the signal varied considerably between individuals, with a skewed distribution pattern, presumably because of differences in the thickness of subcutaneous fat and muscle mass, mean values of EMG activity were calculated using the logarithm of the actual value. However for clarity of presentation in the results these were converted back to microvolts. The maximum amplitude was measured in expiration and in inspiration. Statistical analysis was by the Wilcoxon test for paired data (4).

Results

The study group consisted of seven men and 11 women. Details are given in Table 1. All preoperative

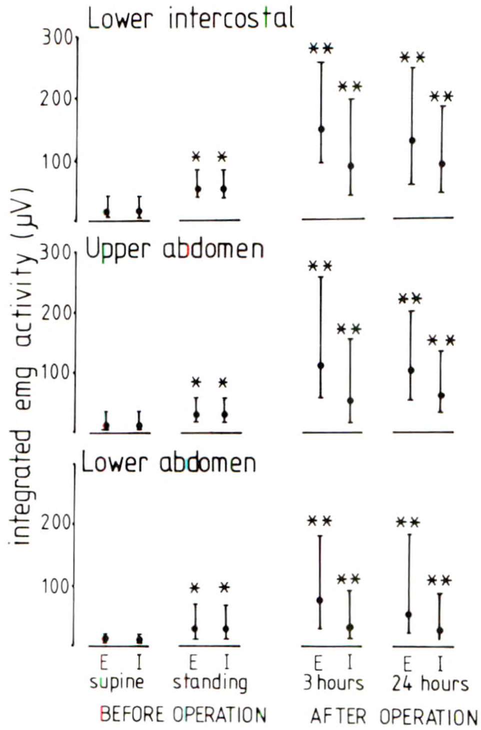

Figure 1. EMG activity before and after UAS. Mean ± SD (bars) averaged EMG potential during inspiration (I) and expiration (E), recorded over a 15-min interval at the times indicated: before surgery, in the supine and standing posture; and after surgery, at 3 hr and 24 hr. Comparisons with before surgery in the supine position: $^*P < 0.05$; $^{**}P < 0.01$

traces in both the supine and standing posture showed some tonic activity only. An increase in EMG activity was observed in each muscle group when the patient was standing (Fig. 1). In some patients in this posture, inspiratory bursts of EMG activity were observed in the lower intercostal recording, which were presumably from the diaphragm.

At both 3 and 24 hr after surgery, with the patient breathing quietly in the supine position, EMG activity was increased. Activity during inspiration was increased by a factor of 3–5 times in each group of muscles, compared with the activity detected in the same position before operation. This activity was slightly greater than that associated with the erect posture before operation (Fig. 1). Superimposed on this increase present during inspiration, most patients showed a further marked increase in activity during expiration. Figure 2 shows a typical postoperative record, demonstrating a progressive increase in EMG activity during expiration with an abrupt decrease at the onset of the next inspiration. Phasic expiratory activity, defined as an increase in activity of more than 20% during expiration, was present in all three EMG recordings in 16 patients at 3 hr after operation, and in 14 patients at 24 hr after operation. Figure 1 sum-

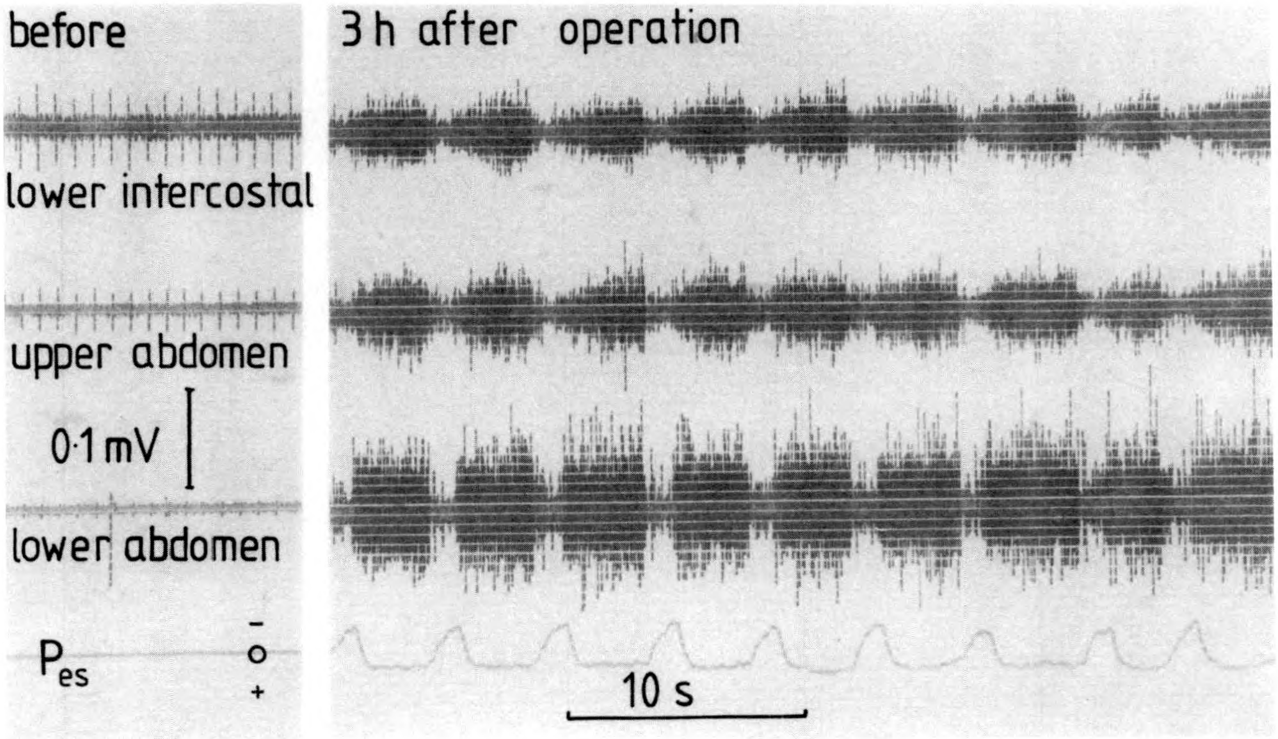

Figure 2. Sample of direct EMG recording from a typical patient before surgery and at 3 hr and at 24 hr after UAS, showing an increase in activity after operation with a phasic respiratory pattern of muscle activity. The trace of esophageal pressure (P_{es}) indicates the phases of respiration (upward deflection is a decrease in pressure).

marises the EMG changes during the study period. Spontaneous postural movement (head raise, turning) or increased arousal of the patient generally caused a further increase in tonic activity and suppressed phasic activity for short periods. In patients with pain sufficient to justify further of opioid analgesia, no obvious influence on the EMG signal was noted after intravenous administration of 5 mg diamorphine, despite increased analgesia reported by these patients.

Discussion

We have demonstrated a marked increase in abdominal and lower intercostal muscle activity after UAS. An increase in abdominal muscle tone will increase in intraabdominal pressure and decrease compliance of the abdominal cavity. In this regard, the lower rib cage and its associated musculature can be considered part of the abdominal container because it encompasses the contents of the upper abdomen (5). The mechanical action of the abdominal muscles is complex (6), and there may be differences in the effects of the muscles that constitute the abdominal wall (7,8). However, a general increase in muscle tone of the abdominal wall will increase intraabdominal pressure, and through a cephalad displacement of the diaphragm, decrease lung volume, unless opposed by a simultaneous tonic increase in inspiratory muscle tone. Additional phasic contraction of the abdominal muscles during expiration would be expected to cause a further reduction in end-expiratory lung volume (7). Previous studies have reported expiratory activity of the abdominal muscles only when minute ventilation is great (8,9,10). Although changes in chest wall properties have been suggested as factors that contribute to the observed postoperative decrease in functional respiratory capacity (FRC) (1), we believe that increased abdominal muscle activity is the only mechanism of this type which has been directly demonstrated. Because there is a greater decrease in FRC after UAS than after lower abdominal surgery (1), it may be interesting to compare postoperative changes in lung volume with the degree of abdominal muscle activity in relation to site of operation.

An important finding of the present study was the observation of phasic expiratory activity of the muscles of the abdominal wall and lower rib cage. There has been recent interest in the possibility that inhibition of the action of the diaphragm may be important in the development of respiratory dysfunction after abdominal surgery, resulting in a search for a valid index of the relative contribution of the diaphragm to breathing. The relative change in anterior posterior dimensions of the rib cage (RC) and abdo-

men (AB) produced by diaphragmatic descent—the ratio $\Delta AB/(\Delta AB + \Delta RC)$—was exploited by Gilbert et al. as an index of diaphragmatic function (11). This index has been reported to show diaphragmatic dysfunction after UAS (11). A further index based on the ability of the contraction of the diaphragm to generate a pressure difference between the thoracic and the abdominal cavities was used by Ford et al. to assess diaphragmatic function (12). This index is obtained by measuring the respiratory swings in gastric pressure (P_{ga}) and pleural pressure (P_{pl}), to obtain the ratio of abdominal to transdiaphragmatic pressure change—$\Delta P_{ga}/\Delta(P_{ga} - P_{pl})$. Using this index, diaphragmatic dysfunction after UAS has been reported by these authors (12), and others (13). However, both these indices attempt to infer the relative actions of two groups of inspiratory muscles, the diaphragm and rib cage muscles, in a system that has contribution to both pressure and movement from a further group of muscles that act on the chest wall, that is those of the abdomen. First, tonic activity of the abdominal muscles will reduce the compliance of the abdomen, and thus the degree of motion of the abdominal wall and change in abdominal pressure caused by diaphragmatic action. Second, the obvious phasic respiratory activity of the abdominal muscles may directly contribute to thoracoabdominal motion, and intraabdominal pressure fluctuations during breathing. Studies in animals (14) and in humans (15) have demonstrated a direct relationship between the electrical activity of the abdominal muscles and abdominal pressure. In this study, although we have demonstrated a phasic respiratory pattern of EMG activity in the abdominal muscles after UAS, no direct measurement of the mechanical influence of this activity was made. However, because we found that EMG activity after UAS was much greater than the activity that occurred in the upright posture before operation (Fig. 1), when the abdominal muscles are known to be active (7), it is reasonable to infer that the influence of this degree of abdominal muscle activity after operation will considerably influence abdominal mechanics and P_{ga} fluctuations. These findings suggest that both the pressure and the motion indices used in previous studies must be interpreted with extreme caution after abdominal surgery, unless the contribution of the abdominal muscles is first taken into account. In addition, because the rib cage, diaphragm, and abdominal muscles may be active at different phases of the respiratory cycle, the time interval over which the pressure and dimensional changes occur has to be assessed most carefully before any change can be attributed to a particular group of muscles.

In conclusion, we have shown that phasic respiratory activity of the lower intercostal and abdominal muscles occurs after UAS. In this situation the mechanical action of these muscles must be considered in the analysis of chest wall motion and respiratory changes in intraabdominal pressure.

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Effects of Progressive Blood Loss on Coagulation as Measured by Thrombelastography

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TUMAN KJ, SPIESS BD, MCCARTHY RJ, IVANKOVICH AD. Effects of progressive blood loss on coagulation as measured by thrombelastography. Anesth Analg 1987;66:856–63.

The effects of progressive blood loss on coagulation were studied in 87 adults (age 23–66 yr) undergoing a variety of operations under general anesthesia. None had preoperative alterations in coagulation or liver function and none were receiving anticoagulant or antiplatelet medication. Whole blood coagulation status was quantitated using thrombelastography (TEG). Blood samples for TEG were obtained 5 min before and 15 min after induction of anesthesia, after each increment of blood loss (EBL) equalling 5% of estimated blood volume (EBV), at the end of surgery, and 2 hr postoperatively. Patients with EBL exceeding 0.15 EBV were given packed red cells and crystalloid solution. Patients with EBL less than 0.15 EBV received only crystalloid. Thrombelastography analysis showed a trend toward increased coagulability with progressive blood loss. Two of four patients with 80% loss of EBV maintained normal to enhanced coagulation status, although the other two developed clinical and thrombelastographic evidence of coagulopathy. Thrombelastography allowed rapid intraoperative diagnosis and specific treatment of loss of platelet activity in the latter two patients. We conclude that during moderate to massive blood loss, use of supplemental fresh frozen plasma and/or platelets should be reserved for patients with documented defects in coagulation. Thrombelastography is useful for the detection and management of coagulation defects associated with intraoperative blood loss.

Key Words: BLOOD, COAGULATION—thrombelastography.

Anesthesiologists frequently encounter cases of blood loss during surgical procedures. These cases range from minimal blood loss requiring no replacement to massive blood loss and many liters of volume replacement and transfusions. Somewhere along this continuum, a point may be reached where enough blood coagulation factors and platelets have been lost, hemodiluted, or had their activity altered that replacement with fresh frozen plasma, cryoprecipitate, and/or platelets is required. Platelet function abnormalities, diffuse intravascular coagulation, or fibrinolysis can occur in many cases of extensive blood loss. The decision to replace coagulation factors and/or platelets is often based on empirically derived, arbitrary standards relating to the number of units of blood transfused, as well as subjective estimates of hemostasis in the surgical field. It is uncommon for prothrombin times, partial thromboplastin times, platelet counts, bleeding times, or levels of fibrinogen or fibrin degradation products to be determined before administering components designed to improve coagulation in the operating room. This omission is probably because tests of coagulation usually are performed outside the operating room and require considerable time to complete.

The thrombelastograph has been shown to be of clinical value in evaluation of whole blood hemostasis in the operating room (1,2). Thrombelastography (TEG) is an easily performed, convenient method of evaluating overall clot reaction; the diagnosis of coagulation factor activity deficiency, platelet abnormalities, dysfibrinogenemias, fibrinolysis, or diffuse intravascular coagulation can all be made from a single thrombelastogram. Thrombelastography is routinely used during hepatic transplantation procedures and has proven useful in coagulation therapy (3,4). Thrombelastography has also been shown to be of great utility in monitoring coagulation in patients undergoing cardiac operations (5). Because blood products are scarce, costly, and not without risk, improved monitoring in the operating room should keep inappropriate use of them to a minimum, thus preventing

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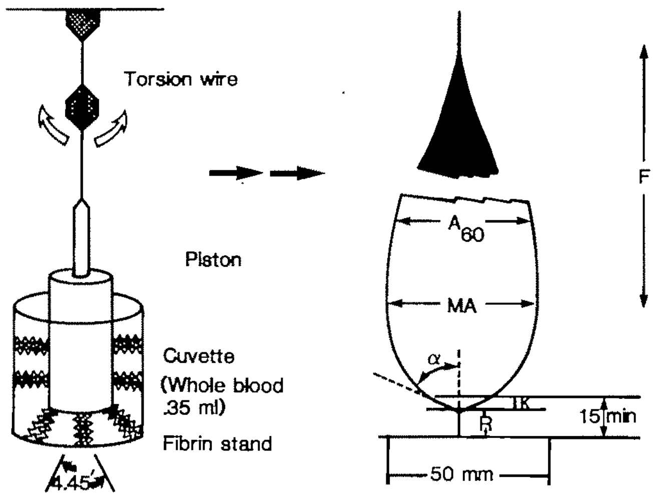

Figure 1. Production of normal thrombelastogram and measured parameters. Abbreviations: R, reaction time, 7–14 min; K value, 3–7 min; α, clot formation rate, 40–60 degrees; MA, maximum amplitude, 40–60 mm; A_{60}, amplitude 60 min after MA; A_{60}/MA, whole blood clot lysis index, >0.85; and F, whole blood clot lysis time, >300 min.

both waste of blood products and morbidity by allowing rapid, specific interventions to be made and avoiding the use of empiric treatment with blood products.

Thrombelastography was developed by Hartert in 1948 (6). The instrument has been used extensively in Europe and has recently achieved increased use in the United States. The principles of the thrombelastograph are simple. Whole blood (0.35 ml) is placed in a metal cuvette, which is rotated. Four drops of mineral oil are spread over the blood surface to prevent evaporation of blood. A piston is suspended in the blood, and as coagulation proceeds, fibrin strands form from the walls of the cuvette to the piston. Shear elasticity is measured as the fibrin transfers motion from the cuvette to the piston and ultimately to a moving pen and paper trace (Fig. 1). Two samples can be run at the same time in most commercially available TEG machines. The TEG machine provides a measurement of clot formation from initial procoagulant activation and fibrin formation through fibrin crosslinking and clot retraction to eventual clot lysis, all from a single blood sample.

The thrombelastograph produces recordings from which several parameters are used to quantitate the whole blood coagulation mechanism (Fig. 1). The reaction time (R value) measures the time from when the blood is placed in the cuvette until an amplitude of 1 mm is reached. The R value (normal 7–14 min) is the time necessary for initial fibrin formation. The K value is defined as the time interval from the end of the R value until the amplitude of the thrombelastograph tracing is 20 mm. The K value (normal 3–7 min) is a measure of the rapidity of fibrin buildup and fibrin crosslinking. The MA, or maximum amplitude (normal 40–60 mm) is a reflection of the absolute strength of the fibrin clot and depends on platelet number and function as well as fibrinogen levels. The α value is measured as the slope of the outside divergence of the tracing from the point of the R value. It is expressed in degrees (normal 40–60°) and also denotes the speed at which clot is being formed and crosslinked. The parameter A_{60} denotes the amplitude 60 min after the MA is measured.

The thrombelastograph provides quantitation of parameters reflecting overall clot reactions and not specific steps in the clotting process. The TEG records the interactions of cellular and humoral components such as red blood cells (RBC), platelets, coagulation factors, and calcium. The values measured from the trace are of diagnostic significance. For example, prolonged R and K values with an MA that is either normal or slightly decreased is an indication of either quantitative or qualitative coagulation factor deficiency or circulating anticoagulants such as heparin. The reaction time (R) is closely related to the activated partial thromboplastin time. The MA value reflects platelet function and activity of factors VIII and XIII. The rate of clot formation (α) primarily reflects the function of fibrinogen and it increases with improved platelet function. A tendency toward an improved coagulation state is reflected by a decrease in R and K values and an increase in MA and α values, as seen at various times during our study. The thrombelastograph can also be used to detect fibrinolysis. Qualitative evidence of significant fibrinolysis can be detected within 30 min as a decreasing MA value. Quantitation of clot lysis can be made by measuring the ratio A_{60}:MA (normal, >85%) or by noting the time from MA until the amplitude returns to zero (whole blood clot lysis time, F; >300 min). The latter parameter is closely related to euglobulin lysis time.

Although TEG is being used more and more frequently for diagnosis and management of perioperative coagulation problems (1–5), there have been no studies evaluating the effects of anesthesia, surgery, blood loss, and fluid replacement on the thrombelastogram. The goal of this study was to characterize the effects of progressive blood loss both with and without packed red cell replacement on the coagulation system as measured by TEG.

Methods

After approval by the institutional Human Investigation Committee, 87 adult patients undergoing ma-

Table 1. TEG Parameters with Crystalloid Replacement of Blood Loss

Parameter	Preinduction	Postinduction	Percent EBV loss 5 (n = 71)	10 (n = 20)	15 (n = 7)	End of case	Two hours after operation
R (min)[a]	12.4 ± 0.8	13.7 ± 0.8	11.3 ± 0.5	11.2 ± 0.9	9.0 ± 1.0	9.8 ± 0.4	9.4 ± 0.5
K (min)[a]	5.1 ± 0.4	5.7 ± 0.3	4.7 ± 0.2	4.5 ± 0.5	4.0 ± 0.5	4.3 ± 0.2	4.5 ± 0.6
α (deg)[a]	44.4 ± 2.0	43.3 ± 1.5	46.3 ± 1.3	47.8 ± 2.7	49.3 ± 3.9	49.1 ± 1.3	49.4 ± 2.0
MA (mm)[a]	55.4 ± 1.6	52.8 ± 1.1	55.3 ± 0.9	56.7 ± 2.0	54.6 ± 3.2	54.6 ± 1.4	48.5 ± 2.4
P' value[b]	—	—	0.003	0.069	0.334	0.002	—
P'' value[c]	—	0.023	—	—	—	—	0.004

R, K, α, and MA defined in text.
[a]Values are mean ± SEM.
[b]P' denotes significance of multivariate analysis of R, K, α, and MA from postinduction values.
[c]P'' denotes same from preinduction values.

jor orthopedic, abdominal, cranial, thoracic, and gynecologic procedures gave informed consent to participate in this study. All patients received general anesthesia with isoflurane or halothane in O_2:N_2O (1:1). Intravenous agents used included etomidate, thiopental, and fentanyl. None of the patients had preoperative alterations in coagulation either clinically or by measurement of prothrombin time, partial thromboplastin time, fibrinogen, and platelet counts. No patients were receiving anticoagulant or antiplatelet medication.

Blood samples for TEG determinations were obtained and analyzed by the same technician 5 min before induction of anesthesia, 15 min after induction of anesthesia, when the estimated blood loss was 5, 10, and 15% of total blood volume (calculated in milliliters as 75 times body weight in kg), at the end of surgery, and 2 hr postoperatively. One group of patients received only crystalloid fluid replacement (group 1, n = 71). Another group with estimated blood loss greater than 0.15 estimated blood volume (EBV) received 1 or more units of packed red blood cells in addition to crystalloid fluid replacement (group 2, n = 16). In group 2, TEG was measured after induction of anesthesia and at various times during blood loss and blood replacement. No patient in group 1 received any blood product. Patients in group 2 received no blood product other than packed red blood cells for replacement of shed hemoglobin. In all patients the total estimated blood loss (EBL) as well as the volume of crystalloid and packed red blood cells administered were recorded at the time each TEG was performed.

The TEG was performed using whole uncitrated blood (0.35 ml) by means of commercially available thrombelastographs (Biclot Elvi 816 Thrombelastograph, Logos Scientific, Henderson, Nevada and Hellige Thrombelastograph, Haemoscope Corporation, Glenview, IL). Measurements of TEG parameters R, K, α, and MA were performed on all samples. The ratio of crystalloid volume replacement to estimated blood volume lost was calculated for each patient and an average value determined at the points where estimated blood loss equaled 5, 10, and 15% of estimated blood volume.

Thrombelastography parameters were considered jointly dependent and analyzed using MANOVA with one repeated measure. Eigenvalues for Wilks' Lambda were determined (7) and evaluated for statistical significance at $P < 0.05$.

Results

The data presented in Table 1 demonstrate that patients tend to become hypocoagulable after induction of general anesthesia when compared to their preanesthetic state (P = 0.023). This finding is reflected by prolongation of R and K values, with a diminution of α and MA values. Moderate blood loss (0.05 EBV) was accompanied by hypercoagulable TEG parameters compared to postanesthesia values (decreased R and K values, increased α and MA values; P = 0.003). An additional increase in coagulability was seen in patients with loss of 0.10 to 0.15 EBV (Fig. 2). At the end of the operation, TEG parameters (R, K, α, MA) remained hypercoagulable compared with levels after induction (P = 0.002). Two hours after the operation TEG parameters remained hypercoagulable compared with those before anesthesia and surgery (P = 0.004). Accounting for fluid deficits from fasting and maintenance crystalloid requirements, the data indicate that crystalloid replacement was associated with euvolemic blood loss in both groups (crystalloid:blood loss calculated as [total crystalloid − 2 $ml \cdot kg^{-1} \cdot hr^{-1}$ of fasting − (4–6) $ml \cdot kg^{-1} \cdot hr^{-1}$ maintenance, depending on surgical trauma]/EBL). Average crystal-

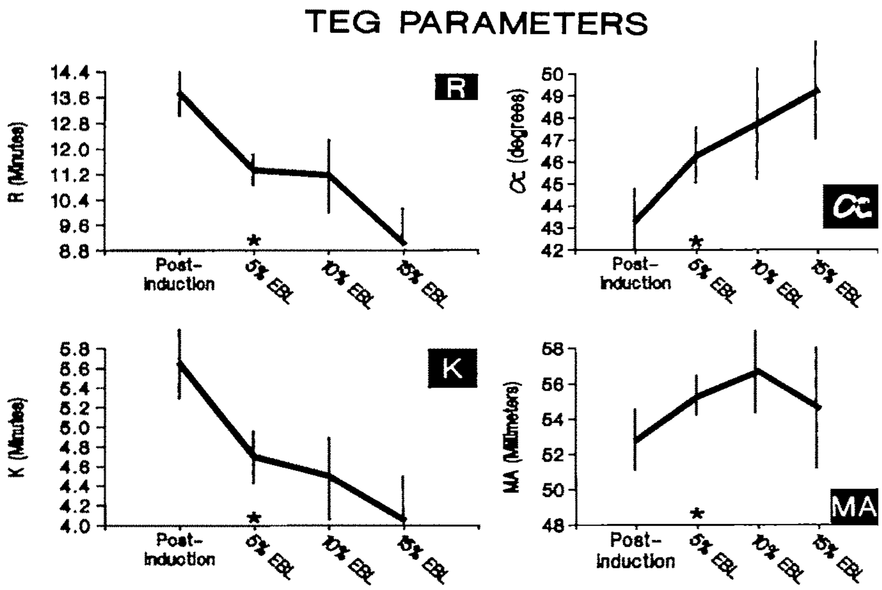

Figure 2. Trends in TEG parameters during progressive blood loss. A pattern of decreasing R and K values with increasing α and MA values is indicative of an accelerated coagulation state (see text).

loid:blood loss ratios were 5.24 at 5%, 5.91 at 10%, and 6.27 at 15% EBV loss, 5.89 at end of surgery and 5.85 in the second postoperative hour.

Table 2 represents data from 16 patients who had blood loss exceeding 15% EBV and who required transfusion with packed red blood cells. Eight of these patients lost between 25 and 35% of EBV and received 2–4 units packed red cell replacement. All of these patients (patients 2, 4, 5, 10, 11, 12, 14, 15) developed an accelerated coagulation state during blood loss that approached 35% EBV (decreased R and K, increased α and MA values). An additional eight patients had blood losses exceeding 50% EBV that required transfusion of 5–10 units packed red cells; this was associated with a progressive increase in coagulability in six of eight patients (75%; patients 3, 7, 8, 9, 13, 16). Four of the patients (patients 1, 3, 6, 7) who lost more than 50% EBV had blood losses that exceeded 80% EBV and required transfusion of packed red blood cells to a total of 9–10 units. Two of these four patients (patients 3 and 7) had a persistent increase in coagulability even after this degree of blood loss (Fig. 3). The other two patients (patients 1 and 6) demonstrated a loss of coagulability by the time 10 units of packed red blood cells had been given. Both of these patients had large decreases in MA values (compared with baseline), small decreases in α values, and values of R and K that were essentially the same as before blood loss. This implied a probable deficit in platelet numbers and/or function, and prompted the transfusion of 8 units of platelets in each patient, which produced a dramatic improvement in the thrombelastographic parameters MA and α (Fig. 4). Patients 1 and 6 developed oozing from multiple raw tissue sites intraoperatively about the time that the tenth unit of blood was being given; this promptly resolved after administration of platelets. No other patients had clinical bleeding that did not appear to represent inadequate surgical hemostasis. Patients in group 2 who lost greater than 15% EBV and developed an increase in coagulability did not have a return of coagulability to baseline levels by the end of surgery. Two hours after the operation, TEG parameters in 13 of these 16 patients (81%) approached levels observed before anesthesia and surgery, whereas three of the 16 (19%; patients 7, 8, 9) remained hypercoagulable.

Discussion

Hemodilution and loss of coagulation factors and platelets during blood loss replaced with crystalloid suggest that a hypocoagulable state might result. Replacement of blood loss with packed red cells that do not contain useful amounts of platelets or coagulation factors would lead one to the same conclusion. This reasoning has stimulated use of blood products such as fresh frozen plasma when treating patients with moderate blood loss. Recent animal studies suggest that recommendations for fresh frozen plasma supplementation (about 1 unit of fresh frozen plasma for every 5–6 units of packed red blood cells) must be questioned (8).

Our clinical study shows no evidence for hypocoagulability as measured by TEG after progressive blood loss. In fact, the coagulation system appears to be stimulated during progressive blood loss. Both

Table 2. TEG Parameters during Blood Loss Exceeding 15% EBV with Packed Red Cell Replacement

Patient number	Parameter[a]	After induction	Percent EBV 15	20	25	30	35	40	45	50	55	60	65	70	75	80	End of case	Two hours after operation
1	R	12	—	—	10	—	7.5	—	—	9	—	10	—	—	—	12	11	12
	K	6	—	—	3.5	—	3	—	—	5	—	6	—	—	—	7.5	4.5	5
	α	40	—	—	53	—	56	—	—	40	—	38	—	—	—	30	48	42
	MA	57	—	—	58	—	57	—	—	49	—	46	—	—	—	34	59	58
	PC	0	—	—	2	—	4	—	—	5	—	7	—	—	—	10	10[b]	10[b]
2	R	10	—	9	—	—	7	—	—	—	—	—	—	—	—	—	8.5	8.5
	K	4	—	4	—	—	3	—	—	—	—	—	—	—	—	—	3.5	3
	α	52	—	56	—	—	55	—	—	—	—	—	—	—	—	—	56	54
	MA	55	—	53	—	—	58	—	—	—	—	—	—	—	—	—	52	52
	PC	0	—	2	—	—	4	—	—	—	—	—	—	—	—	—	4	4
3	R	9.5	—	9	—	—	—	—	11	—	—	9.5	—	—	—	7.5	7.5	8.5
	K	4.5	—	4	—	—	—	—	3.5	—	—	4	—	—	—	2	2	5
	α	53	—	51	—	—	—	—	51	—	—	51	—	—	—	61	61	56
	MA	55	—	56	—	—	—	—	55	—	—	57	—	—	—	64	64	59
	PC	0	—	2	—	—	—	—	5	—	—	7	—	—	—	9	9	9
4	R	9.5	9	—	8	—	5	—	—	—	—	—	—	—	—	—	6	8.5
	K	4.5	4	—	4.5	—	3.5	—	—	—	—	—	—	—	—	—	4	4.5
	α	53	51	—	51	—	52	—	—	—	—	—	—	—	—	—	54	52
	MA	55	56	—	57	—	54	—	—	—	—	—	—	—	—	—	61	56
	PC	0	1	—	2	—	3	—	—	—	—	—	—	—	—	—	5	5
5	R	14	12	—	10.5	—	—	—	—	—	—	—	—	—	—	—	11	13
	K	6	6.5	—	4.5	—	—	—	—	—	—	—	—	—	—	—	5	5.5
	α	35	34	—	49	—	—	—	—	—	—	—	—	—	—	—	48	39
	MA	52	48	—	50	—	—	—	—	—	—	—	—	—	—	—	51	51
	PC	0	1	—	3	—	—	—	—	—	—	—	—	—	—	—	4	4
6	R	14	—	—	—	12	—	—	—	9.5	—	—	10.5	11	—	8.5	8.5	12
	K	6	—	—	—	5	—	—	—	4	—	—	6.5	6	—	3	3	4
	α	38	—	—	—	42	—	—	—	45	—	—	37	34	—	56	56	40
	MA	50	—	—	—	54	—	—	—	58	—	—	48	33	—	55	55	52
	PC	0	—	—	—	3	—	—	—	5	—	—	7	10	—	10[b]	10[b]	10[b]
7	R	13.5	15.5	—	—	12.5	—	—	13.5	10	—	12.5	—	8.5	—	10	10	10
	K	7	5.5	—	—	6	—	—	7.5	5.5	—	5	—	5	—	4	4	4.5
	α	38	39	—	—	45	—	—	36	39	—	48	—	39	—	50	50	46
	MA	51	47	—	—	45	—	—	59	50	—	54	—	53	—	52	52	54
	PC	0	0	—	—	2	—	—	3	4	—	5	—	7	—	10	10	10
8	R	8	10	—	6	—	—	—	—	—	6	—	—	—	—	—	6	7.5
	K	2	3	—	3	—	—	—	—	—	2	—	—	—	—	—	2.5	3
	α	56	59	—	58	—	—	—	—	—	65	—	—	—	—	—	59	62
	MA	54	53	—	58	—	—	—	—	—	64	—	—	—	—	—	63	60
	PC	0	1	—	3	—	—	—	—	—	4	—	—	—	—	—	5	6
9	R	17	14.5	—	14	—	—	—	14	—	11	—	—	—	—	—	11	14
	K	5.5	4.5	—	6	—	—	—	4.5	—	4	—	—	—	—	—	4	4.5
	α	34	41	—	33	—	—	—	37	—	43	—	—	—	—	—	43	31
	MA	44	39	—	48	—	—	—	57	—	57	—	—	—	—	—	57	48
	PC	0	1	—	3	—	—	—	5	—	6	—	—	—	—	—	6	6
10	R	10.5	—	10	—	6.5	—	—	—	—	—	—	—	—	—	—	7	10
	K	2.5	—	3	—	4	—	—	—	—	—	—	—	—	—	—	3.5	3
	α	59	—	60	—	60	—	—	—	—	—	—	—	—	—	—	59	58
	MA	61	—	56	—	60	—	—	—	—	—	—	—	—	—	—	60	60
	PC	0	—	2	—	3	—	—	—	—	—	—	—	—	—	—	3	3
11	R	7	8	—	8.5	—	5.5	—	—	—	—	—	—	—	—	—	5.5	6
	K	3	3.5	—	3	—	3	—	—	—	—	—	—	—	—	—	3	2.5

(continued)

Table 2. TEG Parameters during Blood Loss Exceeding 15% EBV with Packed Red Cell Replacement (*continued*)

Patient number	Parameter[a]	After induction	Percent EBV 15	20	25	30	35	40	45	50	55	60	65	70	75	80	End of case	Two hour after operation
	α	53	55	—	53	—	59	—	—	—	—	—	—	—	—	—	60	50
	MA	57	57	—	58	—	55	—	—	—	—	—	—	—	—	—	58	52
	PC	0	2	—	3	—	4	—	—	—	—	—	—	—	—	—	4	4
12	R	15	—	10.5	—	8.5	15.5	—	—	—	—	—	—	—	—	—	15.5	16
	K	6	—	3.5	—	2.5	3	—	—	—	—	—	—	—	—	—	3	3
	α	38	—	28	—	32	39	—	—	—	—	—	—	—	—	—	39	40
	MA	55	—	67	—	63	57	—	—	—	—	—	—	—	—	—	58	54
	PC	0	—	2	—	3	4	—	—	—	—	—	—	—	—	—	4	4
13	R	11.5	7.5	—	—	—	7.5	—	—	—	5.5	7	—	—	—	—	7.5	11
	K	6	5	—	—	—	4	—	—	—	4	4.5	—	—	—	—	4.5	5
	α	37	43	—	—	—	50	—	—	—	53	45	—	—	—	—	41	39
	MA	41	43	—	—	—	47	—	—	—	48	46	—	—	—	—	46	48
	PC	0	1	—	—	—	3	—	—	—	4	6	—	—	—	—	6	6
14	R	14.5	13.5	11	12	10.5	—	—	—	—	—	—	—	—	—	—	11	14
	K	5	5	4.5	5	4.5	—	—	—	—	—	—	—	—	—	—	4.5	5
	α	44	37	44	44	45	—	—	—	—	—	—	—	—	—	—	46	46
	MA	50	51	49	50	51	—	—	—	—	—	—	—	—	—	—	51	52
	PC	0	1	1	2	3	—	—	—	—	—	—	—	—	—	—	3	3
15	R	14.5	9	8	12	—	—	—	—	—	—	—	—	—	—	—	14.5	14
	K	7	2.5	3	4	—	—	—	—	—	—	—	—	—	—	—	6	6
	α	38	60	59	49	—	—	—	—	—	—	—	—	—	—	—	39	39
	MA	47	54	68	56	—	—	—	—	—	—	—	—	—	—	—	59	50
	PC	0	1	1	2	—	—	—	—	—	—	—	—	—	—	—	2	2
16	R	13	10.5	9	9	11	—	—	—	—	11	—	—	—	—	—	12	13
	K	3	2.5	2.5	2.5	2.5	—	—	—	—	2.5	—	—	—	—	—	3	3.5
	α	53	60	63	59	58	—	—	—	—	60	—	—	—	—	—	58	56
	MA	61	63	62	55	67	—	—	—	—	65	—	—	—	—	—	66	62
	PC	0	0	1	2	3	—	—	—	—	3	—	—	—	—	—	3	3

[a]R and K in min, MA in mm, α in degrees, all defined in text; PC is cumulative units packed red blood cells.
[b]Includes transfusion, 8 units platelets cumulatively.

clinical (9) and animal (10) studies have demonstrated that stress produces accelerated coagulability. Increased levels of renin, angiotensin, and catecholamines are likely during progressive blood loss. Platelet adhesiveness increases significantly after angiotensin as well as catecholamine administration (11,12). It is likely that surgical stress, tissue trauma (with release of tissue thromboplastin), and elevations in serum catecholamine levels offset any hypocoagulable tendency resulting from hemodilution and loss of coagulation factors during progressive blood loss. These offsetting factors are probably responsible for the increase in coagulability seen in most of our patients with moderate to massive blood loss. The decrease in coagulation activity after induction of general anesthesia but before the operation may correspond to a decreased level of stress and lower serum catecholamine levels, compared to the unanesthetized preoperative state. Additionally, general anesthetics have been shown to have direct effects on blood coagulation, especially platelet function (13). For these reasons, the TEG changes with progressive blood loss were compared to the TEG parameters after induction of anesthesia, so that the effects of anesthesia would be eliminated. We did not quantitate parameters of clot lysis (A_{60}/MA and F) because none of our patients had any changes noted in TEG amplitude 60 min after MA.

Other studies have demonstrated that during extensive plasma exchange without hypovolemic shock removal of the total circulating plasma volume does not reduce the coagulation protein activity below effective levels (14). Maintenance of adequate levels of proteins involved in coagulation after plasma exchange results from relocation of these factors from the interstitial fluid space and, in the absence of hepatic hypoperfusion, from increased hepatic synthesis and release of procoagulants. This finding suggests that procoagulant activity is usually maintained under normal circumstances during progressive blood

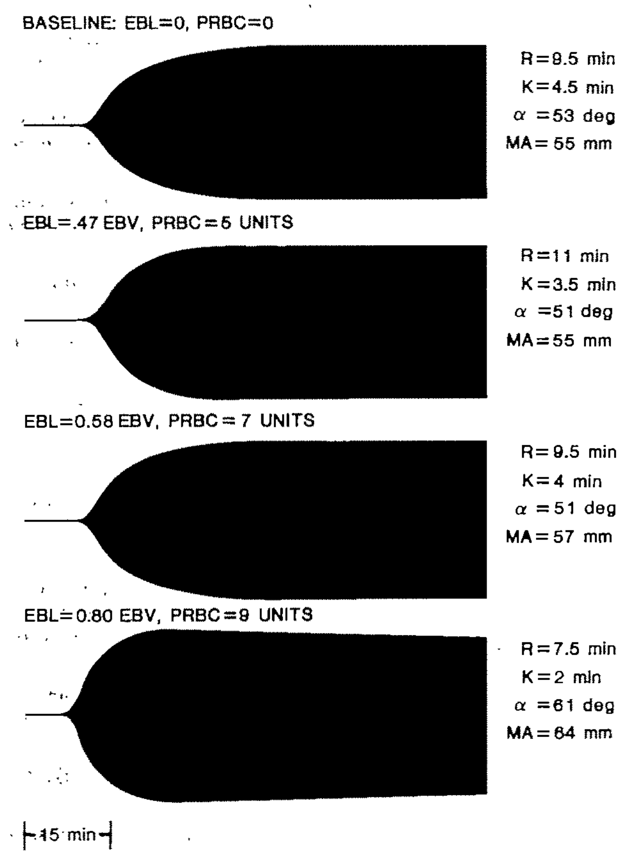

Figure 3. Intraoperative TEGs of a 23-yr-old male undergoing posterior spinal fusion and rod placement for correction of severe scoliosis (patient 3). Blood loss totaled 76% estimated blood volume and required replacement with 9 U packed red blood cells. Progressive hypercoagulability is represented by decreasing R and K values and increasing MA and α values.

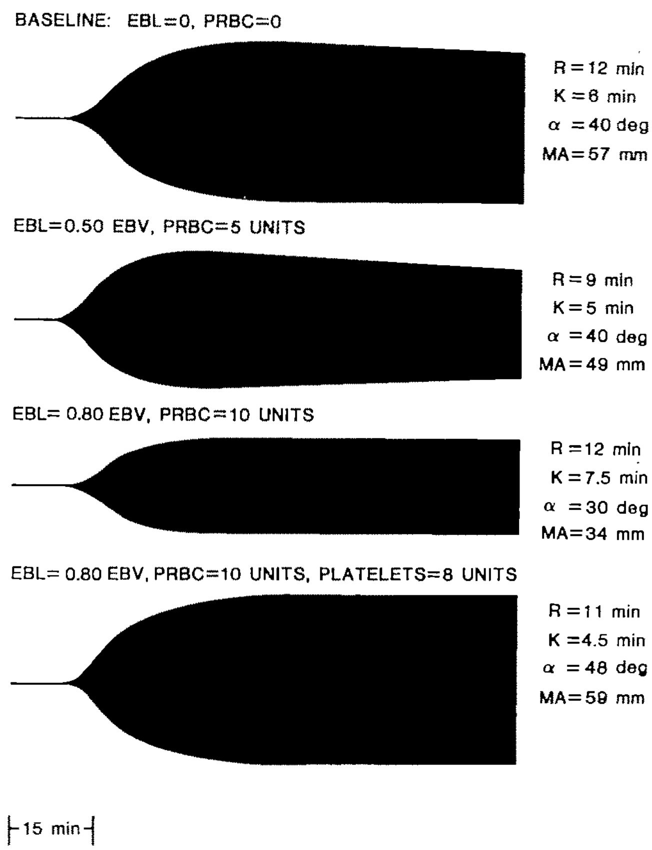

Figure 4. Intraoperative TEGs of a 67-yr-old female undergoing a hip disarticulation and hemipelvectomy for osteosarcoma of the pelvis (patient 1). At the time when blood loss equaled 80% of EBV and 10 U of packed red blood cells had been infused, a sharp decline in MA (and α) values was noted in the TEG that coincided with the onset of a clinical coagulopathy. Infusion of 8 U of platelet concentrate improved MA and α values and hemostasis was achieved.

loss, the first coagulation defect to be found during progressive blood loss being a decrease in platelet number and/or function. Thus, we observed that the four patients in our study who had lost 80% of EBV maintained normal or had shortened R and K values indicative of an increased procoagulant factor activity. The two patients who did develop both clinical and TEG evidence of a coagulopathy had decreased platelet activity (decreased MA values) but normal procoagulant activity (normal R and K values) by the time they had lost 80% of EBV. Whether this was due to decreased platelet number and/or function was not determined in our cases, but the problem was rapidly corrected after infusion of platelets (Fig. 4).

Whatever the exact mechanism for maintenance of normal or even enhanced coagulation during progressive blood loss, this study indicates that there is no justification for routine use of fresh frozen plasma or platelet supplementation during moderate to massive blood loss. It must be emphasized that this conclusion is based on a study of progressive blood loss in patients undergoing a wide range of elective surgical trauma but who had no underlying hepatic dysfunction, sepsis, hematologic disorders, or hypothermia. The presence of these modifying influences on the coagulation system mandates caution in applying the above conclusion universally. Although it appears that coagulation defects do not routinely occur during progressive blood loss (to the levels studied here), when they do occur TEG enables diagnosis of specific problems in the hemostatic system. Such specificity eliminates the need for empiric therapy with blood products that are costly and carry the risk of transmitting hepatitis and possibly other viral infections. Thrombelastography provides a general assessment of blood coagulation status on-site in the operating room within 20–30 min of obtaining a blood sample. These characteristics allow specific goal-directed ther-

apeutic interventions to be instituted more rapidly than do routine coagulation tests, which are usually performed at sites distant from the operating room.

In summary, we have demonstrated that moderate to massive blood loss in patients receiving crystalloid with or without packed red blood cell replacement is not accompanied by a dilutional coagulopathy. In contrast, most patients tend to demonstrate increased coagulation activity as measured by TEG. Although we can only speculate on the reasons for this increase, clearly the use of supplemental fresh frozen plasma and platelets should be reserved for patients with documented defects in coagulation. Thrombelastography provides rapid intraoperative evaluation of all phases of coagulation activity and hence is of great utility in determining the need for and specific type of blood component therapy during progressive moderate to massive blood loss.

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Hemodynamic Effects of Portal Triad Clamping in Humans

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DELVA E, CAMUS Y, PAUGAM C, PARC R, HUGUET C, LIENHART A. Hemodynamic effects of portal triad clamping in humans. Anesth Analg 1987;66: 864–8.

The hemodynamic effects of portal triad clamping (PTC) were studied in 48 adult patients scheduled for elective liver resection. Prior to hepatic resection the effects of a short period of PTC (3–5 min) were evaluated in all 48 patients: mean arterial pressure increased 21%, whereas pulmonary capillary wedge pressure and cardiac index decreased 10 and 17%, respectively. Systemic vascular resistance increased 48%. In 34 patients a liver resection was performed during PTC and hemodynamic measurements were repeated throughout the duration of liver ischemia, which ranged from 14 to 68 min. Hemodynamic changes occurred in the first 3 min and persisted thereafter. After releasing the clamp, hemodynamic parameters returned to initial values in 3 min. These results confirm that PTC does not induce the cardiovascular collapse in humans that it does in common laboratory animals and demonstrate that humans tolerate PTC for periods up to 1 hr.

Key Words: LIVER—blood flow. SURGERY—hepatic.

As early as 1856 and 1859, Oré (1) and Claude Bernard (2) showed that acute ligation of the portal vein in dogs resulted in rapid cardiovascular collapse and death within an hour. The results of these animal experiments were applied directly to man and for many decades it was commonly believed that sudden and complete occlusion of the portal vein was promptly fatal. In 1950 Child et al. (3) demonstrated that the hemodynamic response to acute portal vein occlusion in the monkey was clearly different from that in the dog and that primates and human beings can survive acute ligation of the portal vein. This finding together with the recent concept (4,5) that the liver can tolerate normothermic ischemia for an hour or more accounts for the frequent use nowadays of temporary hepatic inflow occlusion during major liver surgery, as proposed by Pringle (6), in order to minimize blood loss. In surgery, hepatic inflow occlusion is performed by portal triad clamping (PTC): cross-clamping of both the portal vein and the hepatic artery together with the common bile duct.

Experience with liver transplantation has confirmed that hepatic inflow occlusion is tolerated in humans during the anhepatic phase, which induces a 50% decrease in cardiac output (7,8). But this procedure also includes occlusion of the inferior vena cava and little information is available on the hemodynamic effects of hepatic inflow occlusion in humans without occlusion of the inferior vena cava. The purpose of this study is to investigate the hemodynamic changes during PTC in patients anesthetized for liver resection.

Materials and Methods

Between January 1983 and July 1985, 48 patients (25 men and 23 women) scheduled for liver resection were studied according to a protocol approved by the local committee on human research. Informed consent was obtained preoperatively. Age ranged from 19 to 73 yr, averaging 55 yr. In 27 patients, ASA physical status was I, 18 patients were physical status II, and three were physical status III. Only six patients had portal venous hypertension (five with postnecrotic cirrhosis and one with hemochromatosis). All patients were premedicated with diazepam and atropine. Anesthesia, induced with thiopental followed by pancuronium, was maintained with narcotic, pancuronium, and endotracheal 60% nitrous oxide in oxygen. In addition 20 patients received droperidol (0.15 ± 0.02 mg/kg) and 14 received enflurane (0.4–0.8%). Ventilation was controlled throughout anesthesia. The mean

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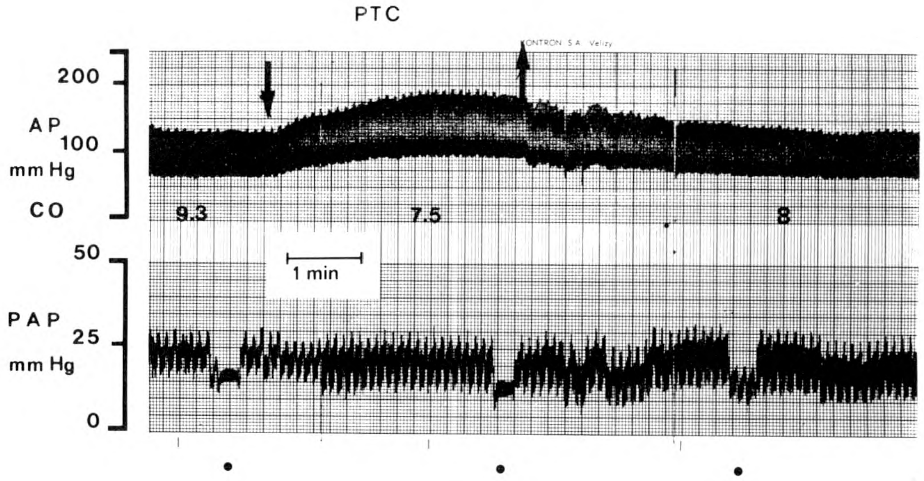

Figure 1. A typical response to 3–5 min PTC. ●, PCWP.

Table 1. Hemodynamic Effects of 3–5 Min Portal Triad Clamping

	Before clamping	During clamping	Percent change
Heart rate (beats/min)	82.6 ± 1.8	85.0 ± 2.1[a]	↑ 3 ± 1
Systolic arterial pressure (mm Hg)	130 ± 3	152 ± 4[a]	↑ 18 ± 2
Diastolic arterial pressure (mm Hg)	71 ± 2	87 ± 2[a]	↑ 24 ± 3
Mean arterial pressure (mm Hg)	91 ± 2	109 ± 2[a]	↑ 21 ± 2
Mean pulmonary arterial pressure (mm Hg)	14.1 ± 0.6	12.3 ± 0.6[a]	↓ 12 ± 3
Pulmonary capillary wedge pressure (mm Hg)[b]	8.2 ± 0.6	6.9 ± 0.5[a]	↓ 10 ± 5
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	3.66 ± 0.15	3.02 ± 0.13[a]	↓ 17 ± 2
Stroke index ($ml \cdot m^{-2} \cdot beat^{-1}$)	44.6 ± 1.5	36.1 ± 1.3[a]	↓ 19 ± 2
Systemic vascular resistance (($dynes \cdot sec \cdot cm^{-5}$)	1255 ± 62	1831 ± 89[a]	↑ 48 ± 4
Pulmonary vascular resistance ($dynes \cdot sec \cdot cm^{-5}$)[b]	81.6 ± 5.4	91.7 ± 6.3[a]	↑ 15 ± 5

Values are means ± SEM; $n = 48$.
[a]$P < 0.05$ when compared with values before clamping.
[b]$n = 42$.

± SEM Pa_{CO_2} was 36.9 ± 0.8 mm Hg and the mean ± SEM blood pH was 7.37 ± 0.01.

Vascular variables that were monitored included heart rate (HR), arterial pressure (AP) by radial artery cannulation, pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP in 42 patients), and thermodilution cardiac output (CO) measured with a thermistor-tipped pulmonary artery catheter. All pressures were referenced to the level of the right atrium and were recorded at end expiration.

Before liver resection, the effects of a short, 3–5 min period of PTC were studied in all 48 patients; the clamp was then removed. The clamp was later reapplied in 34 patients to perform liver resection during PTC. The remaining 14 patients were excluded from this part of the study as the extent of the hepatic tumor either precluded surgery or required a more complex vascular exclusion for resection, involving the inferior vena cava. Among 34 liver resections carried out under PTC, 18 were major resections (right, extended right, or left lobectomy) and 16 were minor. Intraoperative blood transfusion averaged 4.6 ± 0.7 units of packed red blood cells. The mean duration of liver ischemia was 33.6 ± 2.2 min (range, 14–68 min). During liver ischemia the mean body temperature was 34.8 ± 0.1°C. Hemodynamic readings were made immediately before PTC; 3, 10, and 20 min after clamping; at the end of PTC; and 3 and 10 min after releasing the clamp (all results expressed as mean ± SEM). Statistical analysis used analysis of variance and Fisher's least significant difference. A P value less than 0.05 was considered statistically significant.

Results

In all but one patient both systolic and diastolic AP increased during PTC. Cardiac index (CI) decreased in all but three patients. Systemic vascular resistance (SVR) increased in all patients. In the six patients with portal hypertension the hemodynamic changes were

not significantly different from those observed in other patients. There were no significant differences in hemodynamic control values and PTC-induced changes between groups based upon anesthetic regimen. Thus the effects of short periods of PTC are presented as a whole in Table 1. In Figure 1 a typical response to a short PTC is presented.

During liver resection under PTC all hemodynamic changes occurred in the first 3 min after PTC and remained essentially unchanged thereafter (Fig. 2). Nevertheless MAP, MPAP, PCWP, and CI were slightly but significantly lower at the end of PTC than at the beginning. After releasing the clamp the hemodynamic parameters returned to initial values in 3 min except for CI, which remained significantly decreased.

Discussion

The cause of death after acute portal vein ligation in animals has been ascribed to septicemia, toxemia, anemia, or liver failure. That the most important factor is reduction in the circulating blood volume was proposed by Claude Bernard (9) as early as 1877. In the dog the AP decreases in the first few minutes after occlusion of the portal vein, reaching a level of 30–40 mm Hg after 10–20 min (10,11) and CO decreases by 60% within 5 min (11). Simultaneously, upstream portal venous pressure promptly increases to AP level and then declines parallel to the AP. Thirty minutes after occlusion the circulating blood volume decreases by about 60% (10). This results from massive pooling of blood in the splanchnic bed in common laboratory animals that have few portosystemic anastomoses. Laboratory animals survive portal occlusion if provision is made for escape of blood from the portal to the systemic circulation by progressive ligation of the portal vein (2) or by an external shunt (5). On the other hand, ligation of the portal vein induces in primates a mild, transient decrease in AP with a persistent gradient between arterial and upstream portal venous pressures (3). Portal venography shows that immediately after ligation the splanchnic blood in primates returns to the systemic circulation by way of pelvic collaterals (3).

Humans have effective portosystemic collateral channels through which the splanchnic blood can return after clamping of the portal vein (3). Thus the increase in resistance to venous return is small and, according to the concepts of Guyton et al. (12), the decrease in venous return and therefore in CO is only modest. Venous shunting after clamping of the portal vein may result in a moderate increase in portal venous pressure and in the volume of blood in the splanchnic bed in humans.

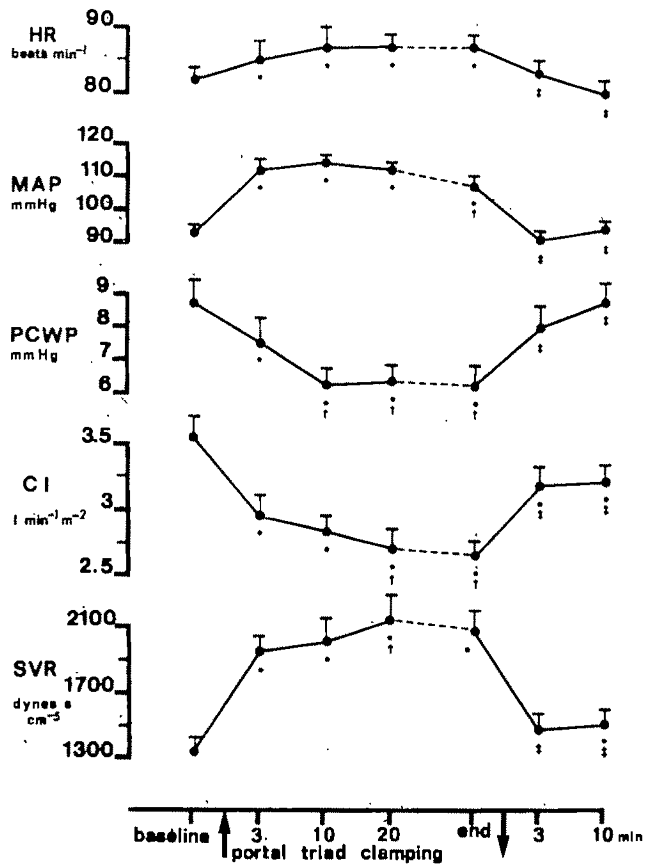

Figure 2. Hemodynamic changes during liver resections with PTC (mean ± SEM for 34 patients; *$P < 0.05$ vs baseline; †$P < 0.05$ vs 3 min after clamping; ‡$P < 0.05$ vs end of PTC).

The cardiovascular effects of temporary hepatic artery occlusion have been little studied in animals or humans. In order to account for the effects of an intravascular redistribution of blood flow, Caldini et al. (13) and Green (14) have proposed a two-compartment model of the systemic circulation, which included a splanchnic channel with a long time constant and a peripheral channel with a short time constant. According to this model occlusion of the hepatic artery may increase the fraction of CO perfusing the peripheral compartment and thus would tend to increase venous return and CO.

Combined occlusion of portal vein and hepatic artery produces the same dramatic cardiovascular consequences in common laboratory animals as does occlusion of the portal vein (15). Our study demonstrates that the hemodynamic response is clearly different in humans. Portal triad clamping induces a mild decrease in CO associated with a small decrease in ventricular filling pressures while AP, surprisingly, in-

creases with a marked increase in SVR. These hemodynamic changes persist during the prolonged PTC needed for liver resection, although MAP, MPAP, PCWP, and CO decrease slightly. The delayed change in capacity of the splanchnic bed shown by Alexander et al. (16) can contribute to a further increase in blood pooling during liver resection, but imbalance between blood loss and transfusion cannot be excluded. In summary, PTC induces in humans small decreases in venous return and CO for periods up to 1 hr. This change greatly differs from the 50% decrease in CO observed when occlusion of the inferior vena cava is combined with hepatic inflow occlusion during liver transplantation (7,8) and liver resection (17).

Mechanical circulatory factors may explain the small decrease in CO, but other mechanisms, nervous or humoral, must be invoked for the often marked increase in AP. Although the results of our study did not show which mechanisms underly the increase in calculated systemic vascular resistance, a number of possibilities can be suggested: 1) The increase in resistance could have been caused by a humoral mechanism such as the vasopressin or the renin–angiotensin systems. However the rapid increase in AP in the first seconds after PTC (Fig. 1), and the rapid decrease in AP after removal of the clamp make such humoral factors an unlikely possibility. 2) Venous pooling in the splanchnic bed tends to reduce thoracic blood volume and so may activate reflexes through cardiopulmonary baroreceptors (18). 3) It is well known that cardiovascular reflexes can be elicited by stimulating receptors in several abdominal organs including liver (19), spleen (20), and portal vein (21). Particularly convincing is the experimental evidence for the existence of pressoreceptors in the portal venous system (21) and in the spleen (20). Activation of these receptors by increasing venous portal pressure (as during PTC) elicits a reflex increase in systemic arterial pressure. On the other hand, crushing the hepatic nerve plexus by a vascular clamp decreases arterial pressure (22). 4) Increasing local venous pressure tends to increase vascular resistance (23). Metabolic, myogenic and reflex mechanisms appear to contribute to this venoarterial response (23–25) that tends to protect against the detrimental effects of excessive capillary pressure (23). Perhaps splanchnic blood flow is preferentially reduced by this increase in vascular pressure thereby minimizing the effects of PTC.

Irrespective of speculation about the nature and the localization of the vascular resistance response, the increase in SVR counteracts the decrease in CO, and AP remains above or at the preclamping level during all periods of PTC we studied.

In conclusion, this study confirms that PTC does not induce in humans the same cardiovascular collapse that it does in common laboratory animals. PTC is well tolerated in humans for periods up to 1 hr and is followed by a prompt hemodynamic recovery after removal of the clamp.

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Neurolytic Celiac Plexus Block for Pancreatic Cancer Pain

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BROWN DL, BULLEY CK, QUIEL EL. Neurolytic celiac plexus block for pancreatic cancer pain. Anesth Analg 1987;66:869–73.

Neurolytic celiac plexus block (NCPB) is an effective method for relief of the pain of pancreatic cancer, but many physicians are reluctant to use the technique because of the perception that the incidence of complications is high. We analyzed the incidence of complications and the quality of pain relief obtained during the use of NCPB in 136 patients with pancreatic cancer. Eighty-five percent of the patients had good pain relief that, in 75% of cases, lasted through the patients' remaining life. No permanent neurologic complications resulted, although two patients had a pneumothorax. Radiographically guided needle placement did not affect quality of pain relief or the incidence of complications. This neurolytic pain block is effective, has a low incidence of neurologic complications, and deserves more widespread use in patients with pancreatic cancer.

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—celiac plexus.

Neurolytic celiac plexus block (NCPB) has been used for many years in alleviating pain caused by intraabdominal malignancies, especially upper abdominal malignancies. Neurolytic celiac plexus block provides useful abdominal pain relief from pancreatic carcinoma in 70–94% of patients, but results in neurologic complications in 1–12% of patients (1,2). The available data include patients with a variety of intraabdominal tumors and even some benign conditions. These data also did not evaluate quality of pain relief or complication rate of NCPB, nor did they specifically study patients with pancreatic cancer. In order to analyze factors related to the quality of pain relief and complications associated with the use of NCPB in patients with pancreatic cancer, multivariant analysis of demographic and clinical variables was done for all patients with pancreatic cancer having NCPB at our institution from 1977 to 1985.

Methods

After approval of the Virginia Mason Medical Center Institutional Review Committee, we reviewed the medical records of all patients with pancreatic cancer receiving alcohol NCPB from the years 1977 to 1985. The variables recorded are listed in Table 1. The quality of the block was graded good or poor according to the patients' comments regarding pain relief, as well as from assessment of analgesic requirements after NCPB. Good pain relief required a positive statement of pain relief by the patient or primary physician or a decrease in analgesic requirements after NCPB. Quality of the block, duration of pain relief and patient survival, and complications after the blocks were determined from both hospital and primary physicians' records.

Patients receiving an NCPB typically underwent diagnostic celiac plexus block with local anesthetic 18–24 hr prior to injection of 50 ml of 50% alcohol. The diagnostic block allowed the patient and physician to assess the adequacy of pain relief and development of side effects before the NCPB. Blocks were performed with patients prone, their abdomens supported by a pillow to reduce the lumbar lordosis. The blocks were performed, typically by resident physicians with attending physician supervision, using the method of Kappis (3) as refined by Moore et al. (4,5) (Fig. 1). Radiographic verification of needle positions for the NCPB varied during the study from no radiographs, to plain films, to computerized tomographic guided needle placement. During the diagnostic blockade, the patients typically did not receive analgesics, which would have made the effectiveness of the local anesthetic blockade difficult to evaluate. However, during injection of the alcohol analgesics were often administered. All patients received supplemental intravenous fluids (principally crystalloids, 10–15 ml/kg as a bolus) at the time of alcohol block. Symptomatic orthostasis required a decrease in mean arterial pressure of greater than 20% of the preblock mean arterial pressure, along with postural light-

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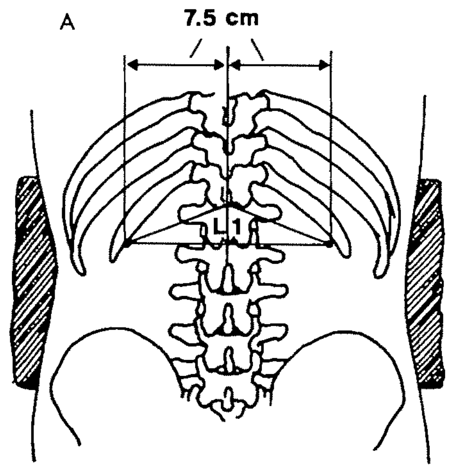
Table 1. Variables Analyzed during Review

Age
Sex
Height
Weight
Weight loss
Metastases
Analgesic use
Therapy
Surgery
Radiation
Chemotherapy
Quality of NCPB pain relief
Number of NCPBs
Radiographic needle guidance for NCPB
Complications from NCPB
Survival after NCPB
Needles used for NCPB



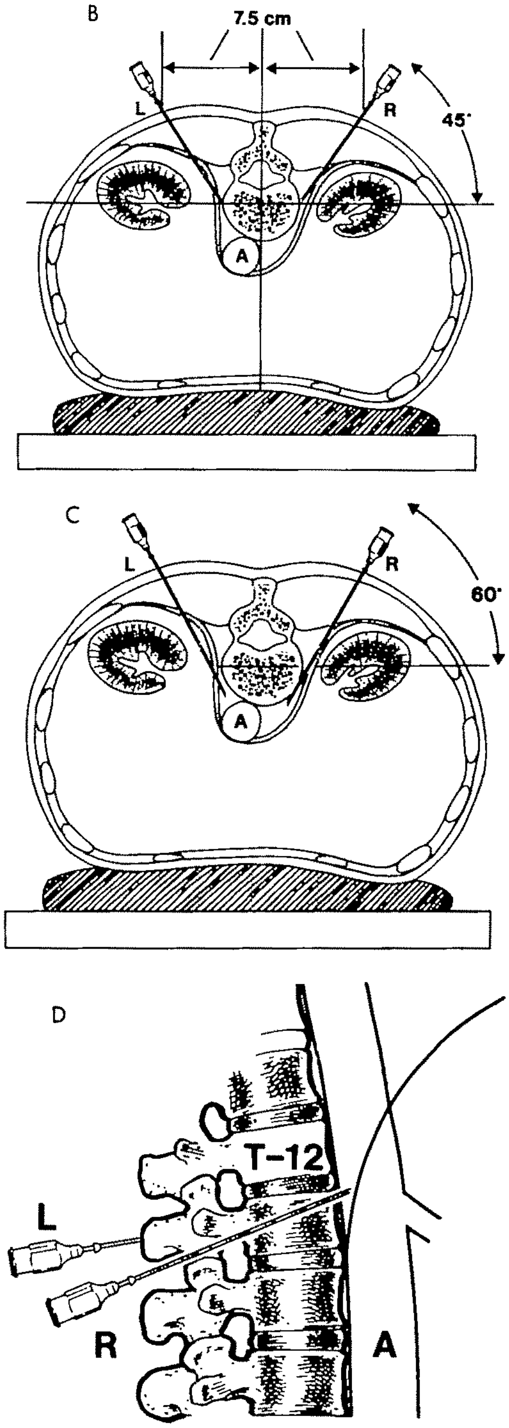


Figure 1. Technique for performing celiac plexus block: (A) needles inserted bilaterally, immediately caudad to the 12th rib, 7.5 cm from the midline; (B) needles are directed 45° from a horizontal plane to contact the L-1 vertebral body; (C) the needles are then redirected by increasing their angle in the horizontal plane, until they slide past the anterior surface of L-1, (D) final needle placement results in the needle tips resting just anterior to the L-1 vertebral body, in a retrocrural position. Abbreviations: A, aorta; L, left needle; R, right needle.

headedness. Repeat NCPB was not considered in cases in which the block was ineffective in relieving pain until approximately 1 week after the original NCPB.

The BMDP statistical program for the IBM personal computer was used for all statistical analyses (6). Statistical significance for two-by-two tables was calculated using the χ^2 test. Statistical significance for small sample two-by-two tables was done using the Fisher's exact test (7). The Cochran test for linear trend (8) was used on two-by-R tables when the covariate of interest was a categorized continuous variable, such as age or weight loss.

Results

The records of 136 patients with pancreatic cancer who underwent NCPB were available for analysis. The patients ranged in age from 29 to 87 years (Table

Table 2. The Effect of Patient Variables on the Quality of Pain Relief Obtained with NCPB

Variable	Percentage of population with good pain relief	P
Age (yr)		0.70[a]
<55	80% (n = 16)	
56–65	90% (n = 43)	
66–75	86% (n = 44)	
>75	76% (n = 13)	
Sex		0.22[b]
Male	89% (n = 67)	
Female	80% (n = 49)	
Metastases (distinct from pancreas)		0.97[b]
None	85% (n = 87)	
Present	85% (n = 28)	
Operation		0.81[b]
Laparotomy	87% (n = 59)	
No laparotomy	84% (n = 57)	
Body mass index		0.10[c]
Normal BMI	87% (n = 107)	
Overweight BMI[d]	69% (n = 9)	
Preblock weight loss (kg)		0.97[a]
<5	83% (n = 15)	
6–10	87% (n = 27)	
11–15	86% (n = 25)	
>15	83% (n = 15)	
Verification of needle placement		0.07[b]
None	93% (n = 54)	
Plain films[e]	81% (n = 53)	
CT scan	73% (n = 8)	
Fluoroscopy	50% (n = 1)	
Needle gauge		0.77[b]
20	85% (n = 79)	
21	100% (n = 3)	
22	85% (n = 34)	

[a]χ^2 for trend.
[b]χ^2.
[c]Fischer's exact test.
[d]Overweight BMI: men > 27, women > 26.
[e]Includes both lateral only and posteroanterior plus lateral films.

2). There were 75 men and 61 women. Pain relief is summarized in Table 2. Metastases from the pancreas were present in 33 of 136 patients, but the quality of pain relief was not affected by their presence (Table 2). The distribution of the metastases is given in Table 3. The effect of additional therapy on pain relief after NCPB is shown in Table 4. In overweight patients, as determined by body mass index (BMI), there was a trend, although not statistically significant, toward less successful pain relief than in patients with a normal BMI (Table 2). The quality of pain relief as affected by preblock weight loss is shown in Table 2. The survival of patients is illustrated in Figure 2.

The quality of pain relief as influenced by the method of radiographic verification of needle placement and by needle gauge is also shown in Table 2. The quality of pain relief obtained when a second NCPB was performed is shown in Table 5. Stratification of patient survival after the first NCPB demonstrated that, when pain relief with the first block was obtained, pain relief lasted throughout the patient's remaining life in 75% of cases and for more than 50% of survival time in an additional 12.5% of cases. Of the 136 NCPBs, the diagnostic and alcohol block were separated by more than 18 hr in 117 patients (86%). Two patients had the diagnostic and alcohol blocks on the same day, and 17 patients (12%) received only the alcohol block without a preliminary diagnostic block. Morbidity from the NCPB occurred in two patients when pneumothorax developed after the block, one during plain film needle guidance and one without radiographic guidance. Neither patient required tube thoracostomy for the pneumothorax. No neurologic injury occurred, although in one patient cerebrospinal fluid was obtained during diagnostic needle placement and in another epidural anesthesia was produced during diagnostic blockade. Eight of the patients developed symptomatic orthostasis after the blocks, necessitating additional fluid therapy, and two patients required hospitalization for orthostatic symptoms. One patient developed congestive heart failure after intravenous fluid administration at the time of NCPB, which resolved with diuresis. No medicolegal claims resulted from these NCPBs.

Discussion

Pancreatic cancer patients undergoing NCPB at our institution received pain relief in 85% of cases, which is similar to the pain relief reported by others using NCPB for intraabdominal malignancies (1,2,9,10). The duration of survival in our patients after the NCPB is consistent with the survival expected in patients with pancreatic cancer. Additionally, the age and sex stratification of our patients is similar to other series of pancreatic cancer patients, suggesting our series of pancreatic cancer patients is a representative one (11). Our analysis of NCPB in these patients with pancreatic cancer allows more complete assessment of variables that are difficult to analyze when the patient population undergoing NCPB is heterogenous.

Most of the variables analyzed in the present study did not clinically affect the quality of NCPB pain relief. Patient age, gender, and weight loss before NCPB did not influence the quality of NCPB pain relief. Additionally, a history of laparotomy, chemotherapy, radiotherapy, or some combination of these therapies did not affect pain relief with NCPB. Similarly, the presence of pancreatic metastases did not influence

Table 3. Effect of Metastases from Pancreatic Cancer on Quality of Pain Relief Obtained with NCPB[a]

	Metastatic site						
Quality	None	L	UA	RP	NUA	B	Total
Good	87 (84%)	15 (79%)	6 (100%)	1 (100%)	5 (83%)	1 (100%)	115 (85%)
Poor	16 (16%)	4 (21%)	0	0	1 (17%)	0	21 (15%)
Total	103 (76%)	19 (14%)	6 (4%)	1 (1%)	6 (4%)	1 (1%)	136 (100%)

Abbreviations: L, liver; UA, upper abdomen; RP, retroperitoneum (distinct from pancreas); NUA, other intraabdominal site; B, bone.
[a] $P = 0.86$ with χ^2.

Table 4. The Influence of Additional Therapy on Pain Relief with NCPB[a]

	Therapy								
Quality	None	S	C	R	SC	SR	CR	SCR	Total
Good	26 (79%)	35 (88%)	24 (86%)	1 (100%)	14 (82%)	4 (80%)	6 (100%)	6 (100%)	116 (85%)
Poor	7 (21%)	5 (12%)	4 (14%)	0	3 (18%)	1 (20%)	0	0	20 (15%)
Total	33 (24%)	40 (29%)	28 (21%)	1 (1%)	17 (12%)	5 (4%)	6 (4%)	6 (4%)	136

Abbreviations: S, surgery; C, chemotherapy; R, radiotherapy. Combinations of therapies use more than one letter.
[a] $P = 0.81$ with χ^2.

the success of the block. Thus, extent of the pancreatic cancer should not deter one from performing NCPB. Our data also indicate that the suggestion (12) that only 20-gauge rather than 22-gauge needles should be used for NCPB remains unproven.

When the body mass index indicated a patient was overweight, the NCPB success decreased from 87% to 69%. This trend would probably reach statistical significance if the numbers of patients were larger. This observation most likely indicates that needle placement was not as precise in the overweight patients, although that conclusion must remain speculative. In spite of the trend toward a decrease in efficacy, over two-thirds of the overweight patients still benefitted from the NCPB.

The use of radiographic verification of needle position with NCPB did not influence the quality of the block (Table 2). A number of reasons that may not be applicable in other institutions may be responsible for this finding. The use of celiac plexus blocks is not confined to patients with malignancy at our institution; thus experience with the block occurs regularly during its use in combination with intercostal nerve blocks for upper abdominal surgery. Further, during the initial years reviewed, few radiographs were obtained to document needle placement; the increased use of radiographs for needle verification may be related to increased medicolegal concerns rather than proof that improved block quality results. Finally, the use of large volumes, 50 ml of 50% alcohol, for NCPB might allow more latitude in needle placement than if smaller volumes of alcohol were used.

Repetition of the NCPB produced neither lower success rates nor increase in the incidence of complications. When blocks were repeated for recurrence of pain after a successful first block, 81% of the patients again obtained successful pain relief (Table 5—Quality of first NCPB = good). Four patients underwent repeat NCPB in an effort to improve pain relief after poor relief with the first NCPB; in two pain relief was improved (Table 5—Quality of first NCPB = poor). Since analyzing these data, our approach to patients in whom an initial poor result is obtained is to perform the second NCPB with computerized tomography guidance to verify spread of injected solution.

The complications attendant to use of NCPBs should be infrequent if the details of technique are adhered to (5). This conclusion is borne out by the absence of significant neurologic complications in these 136 patients. Because this was a retrospective review, less

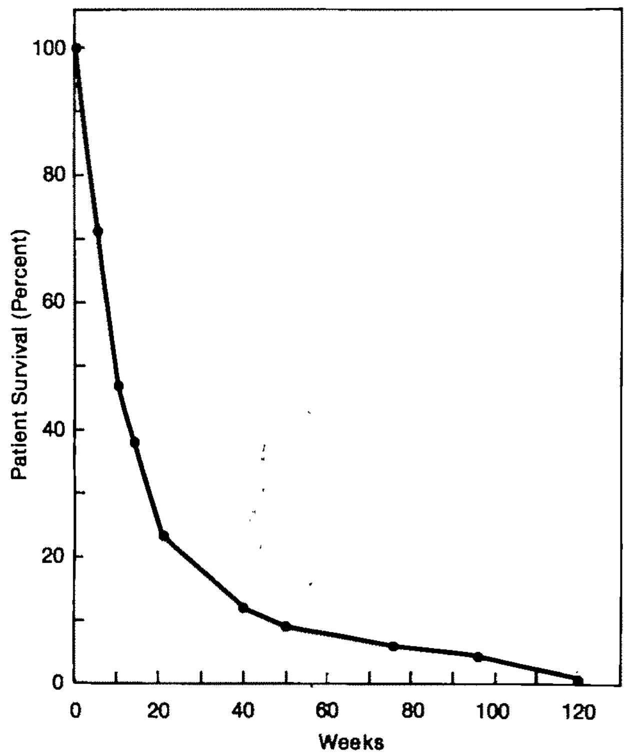


Figure 2. Duration of survival after NCPB in the 136 pancreatic cancer patients reviewed.

significant sensory or motor changes may have occurred without our knowledge; however, access to primary physicians' records makes it unlikely that significant neurologic lesions were missed. Two patients did experience a pneumothorax, and although it is indeterminable from our review, we speculate that the needles were placed between the eleventh and twelfth ribs rather than below the twelfth as the technique calls for. This may occur especially in patients in whom the twelfth rib is rudimentary and difficult to palpate. In both cases of pneumothorax, tube thoracostomy was not necessary, and each resolved spontaneously.

In conclusion, because of the limited survival (months) and minimal therapeutic options in patients with pancreatic cancer, these data support the concept that pain relief in patients with pancreatic cancer is possible and NCPB deserves more widespread use and study. Furthermore, in spite of the success and

Table 5. Quality of Pain Relief Obtained with Second NCPB in 20 Patients Stratified to Pain Relief Quality Obtained with First NCPB[a]

	Second block relief	
Quality of First NCPB	Good	Poor
Good	13 (81%)	3 (19%)
Poor	2 (50%)	2 (50%)
Total	15 (75%)	5 (25%)

[a]$P = 0.25$ with Fischer's exact test.

clinically insignificant complications with NCPB at our institution during this series, radiography-assisted needle placement may be found useful to those physicians desiring medicolegal documentation of needle placement, or in overweight patients.

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1987;66:874–8

Changes in Anterior Fontanel Pressure in Preterm Neonates during Tracheal Intubation

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FRIESEN RH, HONDA AT, THIEME RE. Changes in anterior fontanel pressure in preterm neonates during tracheal intubation. Anesth Analg 1987;66:874–8.

Anterior fontanel pressure (AFP), a noninvasive indicator of intracranial pressure (ICP), was monitored during tracheal intubation in two groups of preterm neonates without neurologic disease. Anterior fontanel pressure was monitored and recorded continuously with a Ladd AFP monitor. Systolic and mean blood pressures were recorded at 1-min intervals. In group 1 (n = 6) patients, 0.02 mg/kg intravenous atropine was administered and awake intubation was performed. Group 2 (n = 6) patients received 0.02 mg/kg intravenous atropine and 0.1 mg/kg pancuronium and one of four anesthetics—0.75% isoflurane, 0.5% halothane, 20 μg/kg fentanyl, or 2 mg/kg ketamine—with intubation after 10 min of mask ventilation. In group 1, AFP increased from 7.7 cm H_2O to 23.8 cm H_2O ($P < 0.05$); the mean increase in AFP was 197%. Anterior fontanel pressure did not change significantly in group 2. Significant increases in AFP may increase the risk of intraventricular hemorrhage in preterm neonates. The present data indicate that indirectly measured ICP increases significantly during awake tracheal intubation in preterm neonates and that this increase can be prevented by prior administration of pancuronium and a general anesthetic.

Key Words: ANESTHESIA—pediatric. INTUBATION—tracheal. BRAIN—intracranial pressure.

Tracheal intubation is a frequently employed procedure in preterm neonates. Although hyaline membrane disease, occurring in up to 60% of preterm neonates (1), is the most common indication, other diseases, as well as anesthetic administration, may require intubation for their management.

Intraventricular hemorrhage, a significant cause of morbidity and mortality, occurs in about 40% of preterm neonates (2–5). One of the many factors associated with development of intraventricular hemorrhage (4–9) is increased anterior fontanel pressure (AFP) (8,9), an indirect monitor of intracranial pressure (ICP). Because tracheal suctioning in unanesthetized preterm neonates increases AFP (10), we postulated that tracheal intubation would have a similar effect. Accordingly, this prospective study was undertaken to monitor changes in AFP in preterm neonates during intubation while awake or anesthetized.

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Methods

Twelve preterm neonates (conceptual age, <37 weeks; weight, <2500 g) requiring a variety of surgical procedures were studied prospectively. This study was approved by the institutional review board; written informed consent was obtained from parents of the subjects. All patients were ASA physical status 3; none had neurologic disease. Characteristics of the patient population are shown in Table 1.

We measured AFP with the Ladd monitor (Ladd Research Industries, Inc., Burlington, VT). This pressure transducer was designed for noninvasive ICP monitoring and uses a fiberoptic sensor and a pneumatic tube and bellows operating on the applanation principle. The principle and the monitor have been previously described (11–13). Acceptable accuracy and correlation with directly measured ICP have been demonstrated (8,11,14,15). We used the Ladd 10004 sensor, the Ladd M1000 pressure monitor, and a Ladd recorder.

On arrival in the operating room, the patient's scalp over the anterior fontanel was shaved, and tincture of benzoin was applied to the surrounding skin. Because application force of the Ladd sensor can affect the accuracy of its measurements (16,17), we used the application technique described by Hill and Volpe (15).

Table 1. Patient Population

	Conceptual age (weeks)	Postnatal age (days)	Weight (g)
Group 1			
Mean ± SD	33.7 ± 2.8	16.0 ± 7.0	1725 ± 466
Range	28–35	8–25	920–2250
Group 2			
Mean ± SD	34.2 ± 1.6	9.8 ± 9.7	1552 ± 346
Range	32–36	1–24	1220–2200

n = 6 in each group.

This technique, which uses adhesive foam to secure the sensor over the anterior fontanel, is both accurate and reliable (15).

Heart rate, systolic blood pressure, and mean blood pressure were recorded at 1-min intervals using a Dinamap 847 monitor and printer (Critikon, Inc., Tampa, FL).

Atropine, 0.02 mg/kg, was administered intravenously to all patients. Intravenous fluids and infusion rates were maintained at preoperative levels, which varied according to the patients' diseases and preoperative conditions. The patients breathed a mixture of air and oxygen with F_{IO_2} appropriate for each patient through a face mask that was gently applied to avoid affecting AFP measurement. Radiant heating devices were used to help maintain patient temperature. Using a table of random numbers, the patients were then divided into two similar groups (Table 1). Group 1 patients were not moved or otherwise disturbed while AFP monitoring continued. This was designated the baseline period. After AFP had been stable for 5 min, awake laryngoscopy and tracheal intubation were performed. Immediately after intubation, 0.1 mg/kg intravenous pancuronium and an anesthetic were administered. One of four anesthetics was chosen using a table of random numbers: 0.75% isoflurane (one patient), halothane 0.5% (two patients), 20 μg/kg fentanyl (one patient), or 2 mg/kg ketamine (two patients). Ventilation with air and oxygen was controlled manually using a nonrebreathing system (Jackson Rees' modification of Ayre's T-piece) such that transcutaneous P_{CO_2} (Novametrix Medical Systems, Inc., Wallingford, CT) was maintained around 35% and Sa_{O_2} (Nellcor, Hayward, CA) between 90–92%. After five more minutes of AFP monitoring, the patients were positioned for the operation and data collection for the study ceased.

Group 2 patients received 0.1 mg/kg intravenous pancuronium and one of the four anesthetics described for group 1: isoflurane (three patients), halothane (one patient), fentanyl (one patient), and ketamine (one patient). The patients were not moved or otherwise disturbed while ventilation was maintained and monitored as in group 1 through a gently applied mask for 10 min, the last 5 min of which was designated the baseline period. Laryngoscopy and tracheal intubation were then performed. After five more minutes of AFP monitoring, data collection for the study ceased, and the patients were positioned for operation.

Table 2. Changes in Anterior Fontanel Pressure, Systolic Blood Pressure, and Mean Blood Pressure during Tracheal Intubation in Preterm Neonates

	Group 1 (awake)	Group 2 (anesthetized)
Baseline AFP (cm H_2O)	7.7 ± 1.7	5.8 ± 1.2
Postintubation AFP	23.8 ± 15.3[a,b]	7.0 ± 2.3
ΔAFP (%)	+197 ± 158[b]	+25 ± 41
Baseline SAP (mm Hg)	63 ± 7	64 ± 13
Postintubation SAP	74 ± 11[a]	70 ± 16
ΔSAP (%)	+20 ± 14	+10 ± 9
Baseline MAP (mm Hg)	50 ± 8	50 ± 12
Postintubation MAP	58 ± 7	55 ± 18
ΔMAP (%)	+15 ± 14	+10 ± 19

Values are mean ± SD; n = 6 in each group.
Abbreviations: AFP, anterior fontanel pressure; SAP, systolic blood pressure; MAP, mean arterial pressure.
[a]Significantly different from baseline ($P < 0.05$).
[b]Significantly different from other group ($P < 0.05$).

Statistical analysis of the data was carried out using the unpaired t-test to describe the patient population (Table 1) and repeated measures analysis of variance to analyze the changes in AFP and arterial pressures. Statistical significance was assumed when $P < 0.05$.

Results

The results are displayed in Table 2 and Figures 1 and 2. During awake tracheal intubation, AFP increased significantly ($P < 0.05$) from 7.7 cm H_2O to 23.8 cm H_2O. The mean increase in AFP during awake intubation was 197%. The duration of increase in AFP after awake intubation ranged from 6 sec to 90 sec (mean 28 sec). These changes in AFP were significantly different ($P < 0.05$) from those observed in group 2. Anterior fontanel pressure did not change significantly during intubation in anesthetized patients.

Systolic blood pressure increased significantly ($P < 0.05$) by an average of 20% during awake intubation. Changes in blood pressure were not significant during intubation under anesthesia. Duration of laryngoscopy ranged from 5 sec to 30 sec in both groups and was similar in both groups (mean, 22 sec in group 1, 18 sec in group 2).

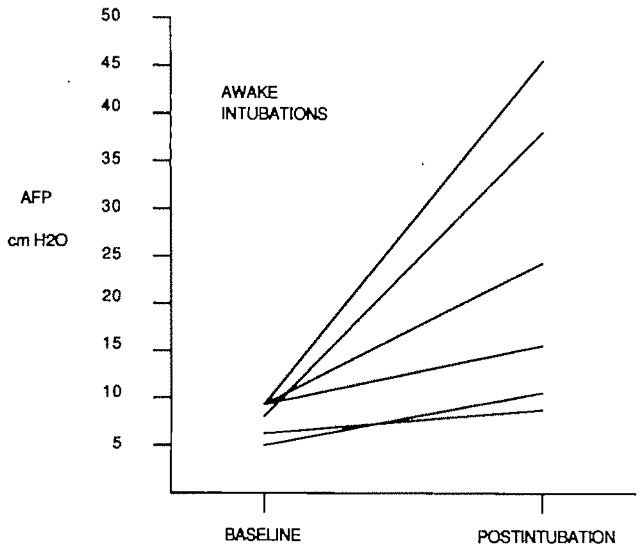

Figure 1. Changes in anterior fontanel pressure in six preterm neonates during awake tracheal intubation.

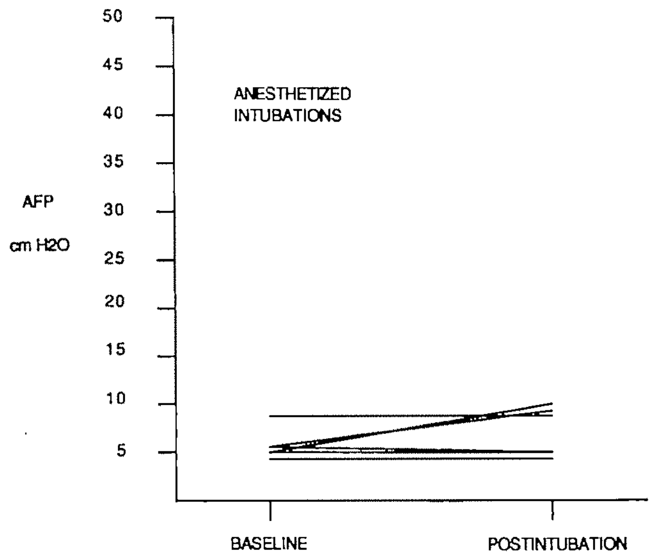

Figure 2. Changes in anterior fontanel pressure in six preterm neonates during tracheal intubation after administration of pancuronium and a general anesthetic.

Discussion

The data in this study demonstrate that AFP increases significantly during awake tracheal intubation in preterm neonates and that this increase can be prevented by prior administration of pancuronium and one of four general anesthetics. Because AFP is a reliable indicator of ICP (8,11,14,15), we conclude that the ICP of preterm neonates increases significantly during awake intubation.

The mechanism by which AFP increases during awake intubation was not demonstrated during this study, but it appeared to be related to coughing and the sustained forced expiratory efforts that occurred during intubation. Only one patient in group 1 did not react to awake intubation in this way, and his AFP increased only 33% (Fig. 1). None of the patients in group 2 had motor responses to intubation. Presumably, the venous stasis accompanying repeated coughing and sustained forced expiratory efforts increases cerebral blood volume and ICP. The observations of Perlman et al. (18) support this as the mechanism for the increase in AFP. They observed wide fluctuations in cerebral blood flow velocity in preterm neonates whose spontaneous ventilatory efforts were out of synchrony with their mechanical ventilators, and found that muscle relaxation with pancuronium eliminated such fluctuations (18).

We did not attempt to evaluate separately the effects of pancuronium and the anesthetics because we think that clinical management of preterm neonates is better when both are used together. Use of the anesthetics unaccompanied by a muscle relaxant might result in greater cardiovascular depression if higher anesthetic doses were required or in chest wall rigidity if fentanyl is used. In a prior study, we demonstrated that the four anesthetics used cause similar mild decreases in AFP in preterm neonates (19).

The results of this study imply that awake tracheal intubation may increase the risk of intraventricular hemorrhage in preterm neonates. Intraventricular hemorrhage is a multifactorial problem (4–9), but two factors known to be associated with its development are increased AFP (8,9) and fluctuations in cerebral blood flow velocity (18). Indeed, Perlman et al. observed a sharp reduction in both the incidence and severity of intraventricular hemorrhage in preterm neonates in whom fluctuations in cerebral blood flow velocity were eliminated by muscle relaxation with pancuronium (18). We think that administration of pancuronium and a general anesthetic spared our patients in group 2 from exposure to two factors associated with intraventricular hemorrhage that were present during awake intubation in patients in group 1.

Fluctuations in systolic blood pressure greater than 100% are another factor associated with intraventricular hemorrhage (5). The mean increases of 20% in systolic blood pressure in group 1 and 9% in a previous study (20) indicate that such wide fluctuations in blood pressure probably are not common during awake intubation.

None of the patients in this study developed intraventricular hemorrhage. On the other hand, none

had the combination of factors associated with the greatest risk of such a complication, i.e., postnatal age less than 72 hr and conceptual age less than 30 weeks (4,7). Both positive pressure ventilation and tracheal intubation during the first hours of life in such patients have been shown to be associated with intraventricular hemorrhage, but may also only reflect the severity of other associated factors requiring resuscitation (6,7).

Our findings have contributed to our current recommendations for anesthetic management of nonintubated preterm neonates. We think that preterm neonates should be anesthetized and paralyzed prior to tracheal intubation unless a specific indication for awake intubation exists. Both maintenance of the airway and positive pressure ventilation were easy to achieve by mask in our patients. Indications for awake intubation remain the classic ones of difficult airway, gastric or small bowel obstruction, and the unstable or moribund patient; prematurity per se is not an indication for awake intubation.

Recommendations for airway management in the neonatal intensive care unit are not as easy to make. Patients there usually require intubation during periods of clinical deterioration or resuscitation. Traditional indications for anesthetic administration are not usually present. However, more patients at greatest risk for intraventricular hemorrhage are likely to be intubated in the intensive care unit than in the operating room. Therefore, in selected patients serious consideration should be given to the use of pancuronium and mask ventilation before intubation when the expertise and equipment for mask ventilation are available. To minimize the duration of laryngoscopy and the number of attempts at intubation, intubation should be performed by a well qualified person in patients at greatest risk for intraventricular hemorrhage.

Because muscle relaxation and general anesthesia are not always feasible and may add other risks, alternative methods of attenuating the ICP response to tracheal intubation should be investigated. Intravenous lidocaine has been shown to suppress coughing (21) and prevent increases in ICP (22) during intubation in older anesthetized patients; a study of its effects in preterm neonates seems worthwhile.

We conclude that awake tracheal intubation in preterm neonates is accompanied by a significant increase in indirectly measured ICP and may contribute to the risk of intraventricular hemorrhage. Muscle relaxation with pancuronium along with general anesthesia prior to intubation prevents this increase in ICP.

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Respiratory Effects of Nalbuphine and Butorphanol in Anesthetized Patients

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ZUCKER JR, NEUENFELDT T, FREUND PR. Respiratory effects of nalbuphine and butorphanol. Anesth Analg 1987;66:879–81.

A double-blind, randomized study was conducted in 16 patients who were anesthetized with 50% nitrous oxide in oxygen and given either 0.17 mg/kg butorphanol or 0.86 mg/kg nalbuphine, and whose respiratory depression was assessed by the response of minute ventilation to increasing carbon dioxide concentrations. The slopes of the carbon dioxide ventilatory response curves [$\Delta\dot{V}E/\Delta PCO_2(L\cdot min^{-1}\cdot \%CO_2^{-1})$] were 7.45 ± 1.17 with nalbuphine and 2.42 ± 0.56 with butorphanol. Butorphanol caused significantly (P < 0.025) greater respiratory depression than nalbuphine. The results of this study caution against the indiscriminate use of butorphanol in the perianesthetic setting.

Key Words: ANALGESICS—butorphanol, nalbuphine. VENTILATION—analgesics and.

Unlike the classical opioids, analgesics possessing combined agonist–antagonist activity do not appear to produce ventilatory depression in direct proportion to drug dosage. Nalbuphine has a ceiling effect for respiratory depression that is paralleled by its limited analgesic effect (1). Similarly, butorphanol has a respiratory dose–response curve that is flatter than that of morphine (2) and produces less respiratory depression than a compared dose of meperidine (3). Although both these drugs produce less respiratory depression than classic narcotic analgesics, it is not known whether they behave comparably with respect to their effects on respiration. With an apparent increase in the clinical popularity of these two agents, a clearer understanding of their actions is important. This study was performed to compare, in a double-blind fashion, maximal ventilatory depression of equianalgesic dosages of nalbuphine and butorphanol in anesthetized patients.

Methods

With institutional approval, 16 unpremedicated ASA 2 or 3 male patients (age, 54 ± 3 yr) were randomly assigned to receive either nalbuphine or butorphanol as the test drug. All patients were monitored with on-line mass spectrometry in addition to routine monitoring of vital signs and ventilatory variables. Anesthesia was induced with 5 mg/kg thiopental and the patients were paralyzed with 1 mg/kg succinylcholine. Tracheal intubation followed intratracheal administration of 100 mg lidocaine, after which the patients were ventilated with a 50:50 oxygen:nitrous oxide mixture. After 5–6 min of recording baseline spontaneous ventilation, patients were given either 10 mg/70 kg nalbuphine or 2 mg/70 kg butorphanol. Two minutes later twice that dosage was administered and, after a further 2 min, three times the original dosage was administered. The total dosages of nalbuphine and butorphanol were 60 mg/70 kg and 12 mg/70 kg respectively. After recording the spontaneous ventilation 4 min later, the inhaled gas was switched to a separate closed rebreathing system with 5–6 L capacity, containing a gas mixture of 46.5% oxygen, 46.5% nitrous oxide, and 7% carbon dioxide for construction of a CO_2 ventilatory response curve as an index of respiratory depression (4). At the end of the study, isoflurane–oxygen anesthesia was given and the patients were operated upon.

Respiratory variables were measured with a Dräger Spiromed spirometer with inspired and expired gases measured on the Allegheny System for Anesthesia and Respiratory Analysis. A continuous recording of ventilation was made as the CO_2 tension increased progressively over 10–12 mins. Points for construction of the CO_2 response curve were made when the measured inspired CO_2 equalled expired CO_2. The

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Table 1. Summary of Patient Characteristics

	Butorphanol	Nalbuphine
Number and ASA status of subjects	4 of II and 4 of III	3 of II and 5 of III
Average age (yr)	52.6	55.4
Average depression of $\dot{V}E$ after drug[a] (%)	71.2	50.7
Slope of $\Delta\dot{V}E/\Delta PCO_2$[a]	2.42	7.45

[a]Significantly different at $P < 0.025$.

slope of the minute ventilation − CO_2 tension curve [$\Delta\dot{V}E/\Delta PCO_2$ (L/min − percentage CO_2)] was constructed using a linear regression analysis. At the end of the study the code was broken and the slopes of the CO_2 response curves were compared with the *t*-test with $P < 0.05$ regarded as statistically significant.

Results

There was no difference in the age, weight, or resting minute ventilation ($\dot{V}E$) before administration of the test drugs in the two groups. Two minutes after the administration of the last dose of drug the average reduction in $\dot{V}E$ after nalbuphine was 49.3% of the baseline level, whereas after butorphanol it was 28.8% (see Table 1). The slopes of the CO_2 ventilatory response curve [$\Delta\dot{V}E/\Delta PCO_2$ ($L{\cdot}min^{-1}{\cdot}\%CO_2^{-1}$) ± SEM were 7.45 ± 1.17 with nalbuphine and 2.42 ± 0.56 with butorphanol. These results are significantly different for both change in minute ventilation and for CO_2 ventilatory response curves. Two patients given butorphanol had progressive depression of $\dot{V}E$ with each drug bolus. One of these patients became apneic after the second bolus and was excluded from the CO_2 response measurements. He was given no other intravenous drugs during the anesthetic. At the end of the surgical procedure, 2.5 hr later, and after elimination of the isoflurane he was still apneic even after receiving 0.6 mg naloxone. Seven minutes later he was given 2 mg physostigmine with resulting initiation of spontaneous ventilation.

Discussion

There are no previous studies comparing the respiratory effects of nalbuphine with butorphanol. Gal et al. (1) used four successive doses of 0.15 mg/kg nalbuphine, at intervals 30–40 min apart and compared nalbuphine with an identical dosage of morphine. Nagashima et al. (2) used either 0.03 mg/kg or 0.06 mg/kg butorphanol compared with 0.15 mg/kg or 0.3 mg/kg morphine. Kallos et al. (3) compared four divided doses of butorphanol (0.5, 0.5, 1, and 2 mg/70 kg) with meperidine (17.5, 17.5, 35, and 70 mg/70 kg) at 12 min intervals. In an animal experiment that compared the enflurane sparing effect of narcotics (5) multiples of 0.5 mg/kg morphine, 0.1 mg/kg butorphanol, and 0.5 mg/kg nalbuphine were compared. In the absence of comparative pharmacokinetic data, we chose a dosage schedule that would, by incremental boluses over a 6-min interval to a total dosage of nalbuphine 60 mg/70 kg and butorphanol 12 mg/70 kg, allow us theoretically to perform our measurements at a time when levels for both drugs would be above the level to maximally affect respiratory depression. We found greater respiratory depression produced by butorphanol at the compared doses. If the achieved level for nalbuphine were higher than or equal to that of butorphanol, then clearly butorphanol produces a greater respiratory depression. If the achieved level for butorphanol were higher than that of nalbuphine, it would still lead to the same conclusion because there is a clearly documented ceiling to nalbuphine's respiratory depression at dosages over 10 mg/70 kg (1). The same ceiling effect has not been satisfactorily documented with butorphanol.

Previous studies (2,3) underestimated the respiratory depression produced by butorphanol. Significant respiratory depression was found with 2 mg and 4 mg butorphanol in healthy 70 kg volunteers (2), yet the conclusion drawn from the two-point analysis was that the "respiratory dose–response curve of butorphanol was flat." More appropriately, the conclusion from that study should have been that 4 mg/70 kg butorphanol produces less respiratory depression than 20 mg/70 kg morphine. Similarly, the previously reported ceiling respiratory depressant effect of butorphanol (3) was determined 46 min after the start of the drug administration, even though butorphanol has a relatively short duration of action in the small dosages studied (2). The results from the present study indicate a significant difference in the ventilatory depression produced by nalbuphine and butorphanol at the compared dosages, butorphanol being a greater respiratory depressant than nalbuphine. This finding is in keeping with the limited analgesic and respiratory depression produced by nalbuphine (1) and the reported use of butorphanol for balanced anesthesia during coronary bypass surgery (6).

An incidental observation in our study was that of

a patient with profound apnea that must be ascribed to the large dose of butorphanol used in our protocol. The fact that a μ-narcotic antagonist and physostigmine were both required to reverse the respiratory depression has not previously been described. This observation is in keeping with the fact that the respiratory depression is only partially antagonized by naloxone (7). We urge caution in the use of butorphanol in the perianesthetic setting because of its respiratory depressant action.

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Effect of Increasing Amounts of Epinephrine during Isobaric Bupivacaine Spinal Anesthesia in Elderly Patients

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RACLE JP, BENKHADRA A, POY JY, GLEIZAL B. Effect of increasing amounts of epinephrine during isobaric bupivacaine anesthesia in elderly patients. Anesth Analg 1987;66:882–6.

The effects of adding epinephrine to isobaric bupivacaine spinal anesthesia were investigated in 96 ASA class II–III patients aged 75 yr or more scheduled for lower extremity surgery. The subjects were randomly allocated into six groups. All patients received 15 mg bupivacaine plain solution in 4 ml, in the horizontal position. Patients in group 1 received bupivacaine plus 1 ml normal saline; patients in other groups received bupivacaine plus increasing dosages of epinephrine: 0.1 mg (group 2), 0.2 mg (group 3), 0.3 mg (group 4), 0.4 mg (group 5), 0.5 mg (group 6). The segmental level of sensory loss was tested using forceps. The time required for maximal spread of the sensory blockade was significantly 50% greater in group 5 than in group 1. No difference was observed, however, between mean highest levels. Addition of 0.2 mg epinephrine prolonged by a significant 25% regression time to L-2 level. Addition of 0.3 and 0.4 mg epinephrine significantly prolonged two-segment regression time by 36 and 53%, respectively, and regression to L-2 level by 29 and 44%, respectively. Addition of 0.5 mg epinephrine did not result in further prolongation of anesthesia. Motor blockade was also increased by addition of epinephrine. It is concluded that addition of 0.3 mg epinephrine may be useful to increase duration of isobaric bupivacaine spinal anesthesia.

Key Words: ANESTHETIC TECHNIQUES—spinal. SYMPATHETIC NERVOUS SYSTEM—epinephrine.

In 1907 Braun demonstrated that the addition of epinephrine to the spinal local anesthetic solution prolonged the duration of anesthesia, and since then epinephrine has been widely used for this purpose (1–3). However, the efficacy of vasoconstrictors in prolonging duration of bupivacaine spinal anesthesia has been questioned. Moore showed that 0.2 mg epinephrine prolonged the mean duration of satisfactory hyperbaric bupivacaine spinal anesthesia by an average of 48% (4), whereas Chambers et al. found no prolongation of two-segment regression time (5). A decreased effect of epinephrine on duration of bupivacaine has been suggested as being related to the high lipid solubility of bupivacaine (6).

In a recent double-blind study, Racle et al. observed that 0.2 mg epinephrine significantly prolongs the duration of plain bupivacaine spinal anesthesia as measured by time of regression to L-2 without increasing the time for two-segment regression (7).

The present study was undertaken to assess the effect of increasing dosages of epinephrine on the duration of isobaric bupivacaine spinal anesthesia.

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Methods

Ninety-six patients over the age of 75 yr, scheduled for orthopedic lower extremity surgery, were studied. All were in ASA categories II–III. All patients gave informed oral consent after detailed explanation of the procedure. The patients were divided into six groups using a computer-based randomized blind design (8). Patients in group 1 (n = 16) received 0.5% bupivacaine, 3 ml (15 mg), plus 1 ml 0.9% sodium chloride. Those in group 2 (n = 16) received 0.5% bupivacaine, 3 ml, plus 0.1 ml of 1:1000 epinephrine (0.1 mg) and 0.9 ml of normal saline. Group 3 (n = 16) received 0.5% bupivacaine, 3 ml, plus 0.2 ml (0.2 mg) of epinephrine and 0.8 ml of normal saline. Group 4 (n = 16) received 0.5% bupivacaine, 3 ml, plus 0.3 ml (0.3 mg) of epinephrine and 0.7 ml of normal saline. Group 5 (n = 16) received 0.5% bupivacaine, 3 ml, plus 0.4 ml (0.4 mg) of epinephrine and 0.6 ml of normal saline. Group 6 (n = 16) received 0.5% bupivacaine, 3 ml, plus 0.5 ml (0.5 mg) of epinephrine and 0.5 ml of normal saline. The volume of epinephrine was measured using a 1-ml tuberculin syringe.

Table 1. Mean (±SD) Age, Weight, and Height of Patients in Each Group

Variables	Group 1 (BP + normal saline)	Group 2 (BP + 0.1 mg E)	Group 3 (BP + 0.2 mg E)	Group 4 (BP + 0.3 mg E)	Group 5 (BP + 0.4 mg E)	Group 6 (BP + 0.5 mg E)
Sex (number)						
Female	12	12	10	11	12	9
Male	4	4	6	5	4	7
Age (yr)						
Mean	84 ± 7	81 ± 5	81 ± 5	81 ± 7	80 ± 5	80 ± 4
Range	75–94	75–91	75–87	75–95	75–91	75–89
Weight (kg)						
Mean	58 ± 13	63 ± 16	64 ± 16	56 ± 12	58 ± 13	67 ± 11
Range	40–79	40–92	40–92	37–70	37–76	50–79
Height (cm)						
Mean	160 ± 7	160 ± 6	161 ± 8	160 ± 8	160 ± 8	164 ± 9
Range	150–170	148–170	150–172	150–170	150–176	150–178

Abbreviations: BP, bupivacaine; E, epinephrine.

The epinephrine and normal saline were added and mixed thoroughly before injection.

Flunitrazepam, 0.5–1 mg, was given orally as premedication 1.5 hr before surgery. All patients were prehydrated with 300 ml of Ringer's lactate solution given IV. This was repeated 30 min after injection of the spinal anesthetic. The patients were placed in a lateral decubitus position on an operating table horizontal with the floor. Under aseptic conditions, lumbar puncture was performed with a 22- or 19-gauge spinal needle at the L3–4 intervertebral space using either a midline or a paramedian approach. All injections were made at a rate of about 1 ml/4–5 sec, and all solutions were at room temperature when injected. Immediately after injection, the patient was placed in the supine horizontal position for the duration of surgery.

The time at completion of injection of the local anesthetic solution into the subarachnoid space was used as the basis for measurements of all time intervals. The dermatome levels of sensory anesthesia were evaluated by pinching bilaterally in midclavicular line and on the legs with a Pean forceps at 2-min intervals. Sensory anesthesia was considered complete when the patient did not respond to closure of forceps to its first rachet (4). When levels of anesthesia were not bilaterally equal, the higher level was used for statistical purposes (a dermatomal chart was used for each patient to ensure accurate assessment of anesthetic level). Motor blockade was assessed at the same time as sensory levels and tested using criteria described by Bromage et al. (9): 0, no impairment of feet movement; 1, barely able to flex knees, no impairment of feet movement; 2, unable to flex knees, barely able to move feet; 3, unable to move feet or knees. Thereafter, levels of anesthesia and motor block were measured every 30 min until anesthesia regressed to the point when the cutaneous response to clamping in the operative site was identical to that produced by clamping the skin of the forearm, or until 6 hr after injection. The mean time for two-segment regression of anesthesia from its highest level and for recovery to the L-2 segment were recorded. All assessments were made by two anesthetic nurses who were unaware of the drugs used.

Blood pressure and heart rate (sphygmomanometer; Dinamap Critikon) were measured at 2.5-min intervals throughout anesthesia and surgery and every 15 min during recovery. The ECG was monitored continuously during induction of anesthesia and during surgery. Hypotension was treated with IV fluids. If this did not prevent a decrease in systolic blood pressure greater than 30% below levels observed under resting conditions, IV ephedrine sulfate (10–30 mg) was used. Resting blood pressure was determined during the anesthesiologist's preoperative visit the day before surgery (10).

All data are presented as mean ± SEM, together with ranges. Mean values were compared using one-way analysis of variance and appropriate t-test. A value of $P < 0.05$ was considered statistically significant.

Results

No significant differences existed among the groups with regard to age, weight, or height (Table 1).

Sensory Blockade

Mean maximal levels of anesthesia (T11.9–T9.2) were similar in the six groups (Table 2). Wide ranges were

Table 2. Sensory Levels after Intrathecal Administration of Bupivacaine with or without Epinephrine (Mean ± SEM)

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Highest level of anesthesia						
Mean	T10.7 ± 0.4	T11.7 ± 0.4	T9.2 ± 0.6	T10.7 ± 0.6	T10.2 ± 0.5	T11.9 ± 0.4
Range	T12–5	L1–T7	T12–4	L1–T6	L1–T6	L1–T7
Time from injection to highest level (min)						
Mean	9.4 ± 0.7[a]	11.4 ± 1.7	8.9 ± 0.7	13.3 ± 2.5	18.8 ± 3.4[d,f,i]	15.3 ± 2.9
Range	4–16	4–30	4–14	4–30	6–50	4–40
Time for 2-segment regression (min)						
Mean	119 ± 7[b]	143 ± 12	149 ± 13	162 ± 13[c]	182 ± 13[d,f]	170 ± 14[d]
Range	65–165	60–240	75–240	90–270	120–330	60–240
Time for regression to L-2 (min)						
Mean	178 ± 8[b]	196 ± 12	223 ± 9[d]	230 ± 13[d,f]	256 ± 13[e,h]	242 ± 13[e,g]
Range	115–240	135–300	150–290	150–360	170–330	180–360

Significant differences by one way analysis of variance: [a]$P < 0.05$, [b]$P < 0.02$.
Significant differences between groups by appropriate t-test. Other groups vs group 1: [c]$P < 0.02$, [d]$P < 0.01$, [e]$P < 0.001$. Other groups vs group 2: [f]$P < 0.05$, [g]$P < 0.01$, [h]$P < 0.001$. Group 5 vs group 3: [i]$P < 0.01$.

observed in time from injection to achievement of the highest level of sensory anesthesia. However, in group 5 (0.4 mg epinephrine), the mean time from injection to the highest level was a significant 50% greater than in patients in whom no epinephrine was used. The mean times required for two-segment regression of anesthesia and regression to L-2 dermatomal level are shown in Table 2. Addition of 0.1 mg epinephrine to bupivacaine had no significant effect. Addition of 0.2 mg epinephrine prolonged two-segment regression time by 25% (not significant) and regression to L-2 level by 25% (significant). The addition of 0.3 and 0.4 mg epinephrine prolonged two-segment regression time by 36 and 53%, and regression to L-2 level by 29 and 44%, respectively, a significant difference from the regression times of group 1. However, the addition of 0.5 mg epinephrine did not result in a further prolongation of anesthesia, nor were times for two-segment regression and for regression to L-2 significantly different than with 0.4 mg epinephrine.

Motor Blockade

The mean time to onset of grade 3 motor block did not differ significantly between the 6 groups (Table 3). Wide ranges were observed. Addition of 0.2 mg epinephrine to bupivacaine increased by a significant 28% the duration of grade 3 motor block, by similarly significant 23% duration of grade 2 and 16% duration of grade 1. Increasing the dose of epinephrine to 0.4 mg prolonged by 59% duration of grade 3, by 49% duration of grade 2, and by 41% duration of grade 1 motor block, all significantly different than the duration of motor block seen in group 1.

Blood Pressure

Resting blood pressure did not differ significantly between the groups (Table 4). There was no significant difference between the groups in the amount of IV fluids given.

Discussion

The duration of tetracaine spinal anesthesia is prolonged by epinephrine (11,12). The effect of vasoconstrictors on duration of lidocaine spinal anesthesia has been discussed (13,14). Controversy exists also with regard to the effect of vasoconstrictors during bupivacaine spinal anesthesia (4,5). The present study shows that sufficient amounts of epinephrine can prolong the sensory blockade of isobaric bupivacaine spinal anesthesia, as measured by time of two-segment regression and by time to regression to the L-2 level. This is in agreement with a previous study on the effect of 0.2 mg epinephrine added to isobaric bupivacaine (7), and with Moore's study on the effect of hyperbaric bupivacaine with 0.2 mg epinephrine (4). However, Chambers et al., in a double-blind trial (5), found that the addition of 0.2 mg epinephrine to 3 ml of 0.5% bupivacaine in 8% dextrose produced a greater prolongation of the sensory block, although this reached statistical significance only in terms of total duration of anesthesia.

Table 3. Characteristics of the Spinal Motor Block in Different Groups

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Time to onset of total motor block: grade 3 (min)						
Mean	7.6 ± 0.5	8.1 ± 1.5	6.5 ± 0.7	8.8 ± 2	12.9 ± 1.8	8.6 ± 1.5
Range	4–10	4–26	4–12	4–30	4–24	2–24
Duration of grade 3 motor block (min)						
Mean	169 ± 9^{a}	193 ± 12	216 ± 8^{c}	239 ± $13^{c,e}$	269 ± $12^{d,f,h}$	260 ± $13^{d,}$
Range	90–225	120–270	160–270	120–340	180–360	190–360
Duration of grade 2 motor block (min)						
Mean	198 ± 9^{a}	220 ± 12	243 ± 9^{c}	271 ± $13^{d,e}$	295 ± $12^{d,f,h}$	293 ± $12^{d,}$
Range	125–255	135–300	190–300	150–360	195–370	210–360
Duration of grade 1 motor block (min)						
Mean	228 ± 8^{a}	252 ± 12	264 ± 10^{b}	297 ± $12^{d,e}$	322 ± $13^{d,f,i}$	320 ± $12^{d,}$
Range	170–300	180–330	200–330	180–375	200–400	270–410

Significant differences by one way analysis of variance: $^{a}P < 0.02$. Significant differences between groups by appropriate *t*-test. Other groups vs grou 1: $^{b}P < 0.05$, $^{c}P < 0.01$, $^{d}P < 0.001$. Other groups vs group 2: $^{e}P < 0.01$, $^{f}P < 0.001$. Groups 5 and 6 vs group 3: $^{g}P < 0.02$, $^{h}P < 0.01$, $^{i}P < 0.001$.

Table 4. Blood Pressure and Administration of Ephedrine and IV Fluid

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Resting systolic blood pressure (mm Hg)						
Mean	148 ± 6	150 ± 7	151 ± 5	154 ± 4	147 ± 5	137 ± 4
Range	104–200	110–200	110–180	130–190	120–180	110–170
Lowest level of systolic blood pressure (mm Hg)						
Mean	122 ± 7	125 ± 7	120 ± 5	127 ± 6	117 ± 6	104 ± 5
Range	85–180	80–195	80–150	98–170	86–160	76–140
Mean % of resting values	−18 ± 3	−16 ± 3	−21 ± 3	−18 ± 3	−20 ± 3	−24 ± 3
Number of patients receiving ephedrine (%)	5 (31)	1 (6)	6 (38)	4 (25)	8 (50)	7 (44)
Volume of lactated Ringer's solution given (ml/kg)						
Mean	12.5 ± 1.5	9.6 ± 1.2	16.1 ± 1.3	15.3 ± 2.2	14.1 ± 2.3	12.4 ± 1
Range	6.3–25	6.3–25	6.7–25	7.1–40.6	6.6–43.5	5.9–21.:

The present study differs from that reported by Chambers et al. (5) in two ways. First, the local anesthetic solution was hyperbaric in Chambers's study and isobaric in our study. As noted by Chambers et al., it is possible that the use of solutions containing relatively high concentration of dextrose may alter the effect of an added vasoconstrictor. Second, Chambers et al. did not use increasing dosages of epinephrine. In the present study, as in Leicht and Carlson's study on hyperbaric lidocaine (14), time for two-segment regression was significantly prolonged only after addition of 0.3 mg epinephrine.

It has been said that duration of spinal anesthesia is longer in older patients than in younger and that this is due to a decrease in systemic absorption of the local anesthetic (15). Therefore, any additional effect of vasoconstrictors might be minimized in the elderly. However, a recent controlled study in our institutio (16) showed no significant prolongation of times fc two-segment regression or for regression to L-2 lev in comparing 29 patients younger than 50 yr to : patients aged 80 yr or more receiving 3 ml 0.5% bu pivacaine plain solution intrathecally. This is in agre ment with the previous study of Pitkänen et al. (17 However, data of Axelsson et al. (18) do not suppo the hypothesis of a decrease in systemic absorptio of subarachnoid isobaric bupivacaine in older pa tients.

The use of high doses of epinephrine in elderl patients is questionable, as it may compromise ci culation in the spinal cord. Using 5 mg pheny ephrine, equipotent to 0.5 mg epinephrine (12), adde to lidocaine for spinal anesthesia in patients aged 50–8 yr, Vaida et al. (19), however, found no neurotox

effect. Intrathecal injection of epinephrine in dogs has been shown to decrease spinal cord blood flow (20). However, bupivacaine decreases spinal cord blood flow by itself, and the added epinephrine has only a minor effect on spinal circulation in the presence of bupivacaine (21). As during epidural analgesia, prolonged systemic hypotension during spinal anesthesia may itself compromise spinal cord circulation (22).

In the present study, the addition of 0.5 mg epinephrine did not result in a further prolongation of anesthesia, but in fact appeared to result in a slightly shorter duration of sensory anesthesia compared to 0.4 mg of epinephrine. This may indicate a ceiling effect with regard to the effect of epinephrine. Spinally administered epinephrine has been shown to produce sensory analgesia by a direct action on the α-adrenergic inhibitory system of substensia gelatinosa (23). One can postulate that increasing dosages of epinephrine may increase duration of spinal blockade until α-adrenergic receptors are saturated.

In conclusion, in elderly patients, both 0.3 and 0.4 mg epinephrine significantly prolong the duration of spinal anesthesia. There appears to be no statistically significant difference in terms of duration of sensory anesthesia and motor blockade between the use of 0.3 and 0.4 mg epinephrine. As the 0.4-mg dose of epinephrine was associated with the longest onset to maximum spread, it would appear that the 0.3-mg dose of epinephrine would be the more appropriate dose.

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Epidural Butorphanol or Morphine for the Relief of Post-Cesarean Section Pain:

Ventilatory Responses to Carbon Dioxide

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ABBOUD TK, MOORE M, ZHU J, MURAKAWA K, MINEHART M, LONGHITANO M, TERRASI J, KLEPPER ID, CHOI Y, KIMBALL S, CHU G. Epidural butorphanol or morphine for the relief of post-cesarean section pain: ventilatory responses to carbon dioxide. Anesth Analg 1987;66:887–93.

To determine the safety, efficacy, and the ventilatory responses to carbon dioxide (CO_2) of epidurally administered butorphanol or morphine, 122 healthy women who underwent cesarean section with epidural anesthesia were studied. Patients were randomly assigned to receive one of four epidural regimens for the relief of postoperative pain: 5 mg morphine (n = 32), 4 mg butorphanol (n = 30), 2 mg butorphanol (n = 29), or 1 mg butorphanol (n = 31). Epidural morphine provided satisfactory analgesia with slow onset and long duration of approximately 21 hr. When butorphanol was administered, analgesia of rapid onset was seen with increasing duration and effectiveness observed with increasing dose; approximately 8 hr when using 4 mg. Sixty-two percent of the patients who received morphine had pruritus. Somnolence was the main side effect encountered in patients who received epidural butorphanol. The ventilatory response to CO_2 was depressed after morphine and after 2 and 4 mg butorphanol, but the duration of depression was more prolonged after morphine. It is concluded that epidural butorphanol is effective in providing pain relief after cesarean section with minor side effects. However, patients must be observed closely because of possible respiratory depression.

Key Words: ANESTHESIA—obstetrical. ANESTHETIC TECHNIQUES—epidural. ANALGESICS—butorphanol, morphine. PAIN—postoperative.

Epidural administration of morphine produces profound postoperative analgesia (1). However, its use has been associated with the occurrence of undesirable side effects, including pruritus, nausea, vomiting, urinary retention, and respiratory depression. A recent report on the use of epidurally administered butorphanol in post-cesarean section patients indicated the reliable production of analgesia with a lack of undesirable side effects (2). However, an appropriately sensitive method of assessing the respiratory effects was not used.

The present study was undertaken to evaluate the respiratory effects of epidurally administered morphine or butorphanol in more detail using the ventilatory responses to progressive hypercapnia.

Materials and Methods

We studied 122 healthy women at term who underwent cesarean delivery with epidural anesthesia. Patient characteristics were similar with the unimportant exception of maternal weight, which was slightly different among the four groups (Table 1). Informed consent was obtained from each patient and the study was approved by the Committee on Human Research. Complications during pregnancy, major organ disease, or a history of drug abuse excluded a patient from the study.

For anesthesia during cesarean section, 2% lidocaine with 1:200,000 epinephrine was given through a lumbar epidural catheter placed at L2–3 or L3–4. These catheters were left in place after surgery. When patients first requested pain relief after surgery, they

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Table 1. Demographic Data

	Morphine, 5 mg	Butorphanol, 4 mg	Butorphanol, 2 mg	Butorphanol, 1 mg
Maternal age (yr)	27.13 ± 0.21 (n = 32)	26.71 ± 0.19 (n = 30)	27.58 ± 0.17 (n = 29)	26.84 ± 0.17 (n = 31)
Maternal weight (kg)	68.59 ± 0.55 (n = 32)	65.60 ± 0.61[a] (n = 30)	69.21 ± 0.53 (n = 29)	63.35 ± 0.46[a] (n = 31)
Maternal height (cm)	159.13 ± 0.32 (n = 32)	160.30 ± 0.34 (n = 30)	159.13 ± 0.48 (n = 29)	160.55 ± 0.26 (n = 31)

[a]Statistically significant difference compared with the other three groups.
[b]Statistically significant difference compared with the morphine and the 2-mg group.
Values are mean ± SEM.

Table 2. First Dose Pain Relief of ≥50% as Measured on Visual Linear Analog Scale

Treatment group	Onset of pain relief (hr)	Duration of pain relief (hr)	Time before remedication (hr)
Butorphanol, 1 mg (n = 31)	0.37 ± 0.03	4.82 ± 0.77	5.48 ± 0.75
Butorphanol, 2 mg (n = 29)	0.38 ± 0.04	5.53 ± 0.86	6.02 ± 0.80
Butorphanol, 4 mg (n = 30)	0.36 ± 0.04	8.05 ± 0.97	8.48 ± 0.99[b]
Morphine, 5 mg (n = 32)	0.85 ± 0.11[a]	21.17 ± 0.85[a]	22.03 ± 0.83[a]

[a]$P < 0.05$ compared with butorphanol groups.
[b]$P < 0.05$ compared with butorphanol, 1 mg.
Data are mean ± SEM. Time is expressed in hr.

were randomly assigned to receive one of four epidural narcotics in a double-blind fashion: 5 mg morphine (n = 32), 4 mg butorphanol (n = 30), 2 mg butorphanol (n = 29), or 1 mg butorphanol (n = 31). All drugs given were diluted in 10 ml saline solution.

The intensity of pain and pain relief were assessed using a visual linear analog scale (3). This scale consisted of a 100-mm line on which the patient represented the degree of pain she was experiencing by placing a point somewhere between "no pain" and "the worst pain I have ever experienced." Each patient made such an assessment immediately before administration of the drug and again at .25, .5, .75, 1.0, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hr afterwards. Maternal respiratory rate, blood pressure, and heart rate were also measured at the same times. At the end of the 24-hr observation period or at the point of remedication, the patient and the observer each gave a global assessment of the overall effectiveness of the analgesic treatment as follows:

0 = no relief
1 = poor relief
2 = fair relief
3 = good relief
4 = very good relief
5 = excellent relief

Possible respiratory depressant effects of morphine and butorphanol were assessed according to the ventilatory responses to progressive hypercapnia using a modified Read rebreathing technique (4) with a computer-controlled data acquisition system (5) as described later. Baseline measurements were obtained before administration of morphine or butorphanol and repeated at 1½, 3, 6, 12, 16, and 24 hr if the patient stayed in the study. Patients were observed for 24 hr for the appearance of adverse effects, including pruritus, nausea, vomiting, and respiratory depression (i.e., a respiratory rate of <10 breaths/min).

If patients requested additional analgesia, a narcotic was administered intramuscularly and assessments of pain relief and ventilatory measurements were discontinued. Toward the latter part of the study, 16 patients in the three butorphanol groups were given the same dose of butorphanol when pain recurred and patients were evaluated in the same manner as after the first dose.

Statistical analyses of data was performed using 1) analyses of variances for comparison between groups;

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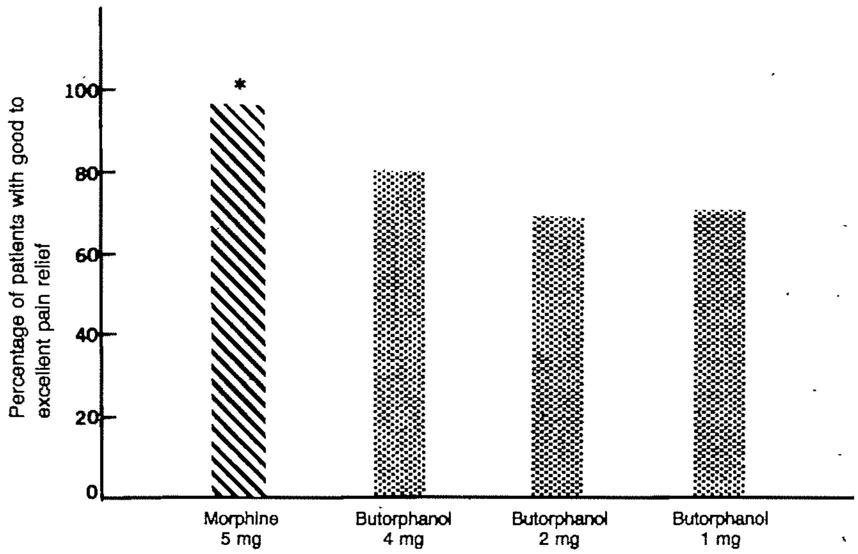

Figure 1. Percentage of patients (as assessed by patients) having good to excellent pain relief after epidural administration of morphine or butorphanol. ($P < 0.05$, morphine vs butorphanol, 1 or 2 mg).

Table 3. Second Dose Pain Relief of ≥50% as Measured on the Visual Linear Analog Scale

Treatment groups	Onset of pain relief (hr)	Duration of pain relief (hr)	Time before remedication (hr)
Butorphanol, 1 mg (n = 6)	0.40 ± 0.10	2.70 ± 1.32	3.83 ± 1.05
Butorphanol, 2 mg (n = 5)	0.38 ± 0.07	5.06 ± 2.37	5.57 ± 2.20
Butorphanol, 4 mg (n = 5)	0.38 ± 0.07	9.00 ± 5.00	9.20 ± 5.10

Time is expressed in hr.
Data are mean ± SEM.

2) paired t-test to compare data to control values within the same group; 3) χ^2-test to compare the incidence of side effects between groups using raw data. Differences were considered statistically significant when $P < 0.05$.

Respiratory Measurements

CO_2 response curves ($\Delta\dot{V}E/\Delta PET_{CO_2}$, when $\dot{V}E$ = minute ventilation (in L/min) and PET_{CO_2} = end-tidal CO_2 (in mm Hg) were measured before and after administration of morphine or butorphanol using a portable, computer-controlled data acquisition system (5). It included an Apple II+ computer and measures $\dot{V}E$, PET_{CO_2}. Each patient rebreathed exhaled CO_2 through a two-way breathing valve attached to a 9-liter reservoir, initially filled with 5% CO_2 and the balance oxygen. Exhaled CO_2 concentrations were measured with a Beckman LB-2 infrared medical gas analyzer on samples taken through a catheter connected at the mouthpiece. The CO_2 response curve was then determined by plotting $\dot{V}E$ vs PET_{CO_2}. The CO_2 response slope was determined by linear regression of the data above an analytically determined breakpoint. We examined both the slope and the position of the slope at PET_{CO_2} 50 ($\dot{V}E_{50}$). The data were stored on discs and could be recalled for editing, plotting, or statistical analyses. The system is portable, thus giving the investigator the flexibility of measuring patient responses in either the recovery room or the ward.

Results

Table 2 represents pain relief data using the visual linear analog scale. Butorphanol provided rapid pain relief in the three groups of patients within 22 ± 2.4 min as compared with morphine, which was associated with an onset time of 51 ± 6.6, mean ± SEM ($P < 0.05$). Duration of pain relief was significantly longer in the morphine group than it was in the three butorphanol groups. Analgesia up to 6–24 hr was

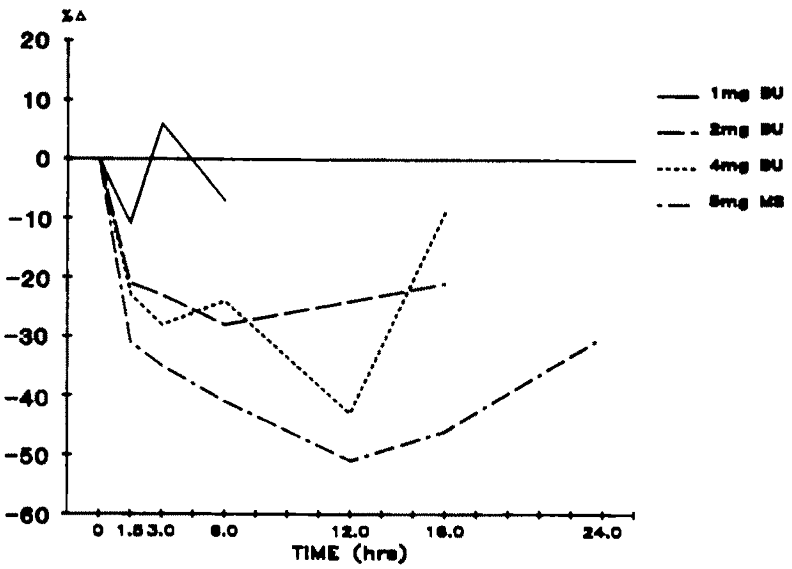

Figure 2. Percent change in CO_2 response slopes ($L \cdot min^{-1} \cdot mm$ Hg) from control values after patients received epidural morphine or butorphanol.

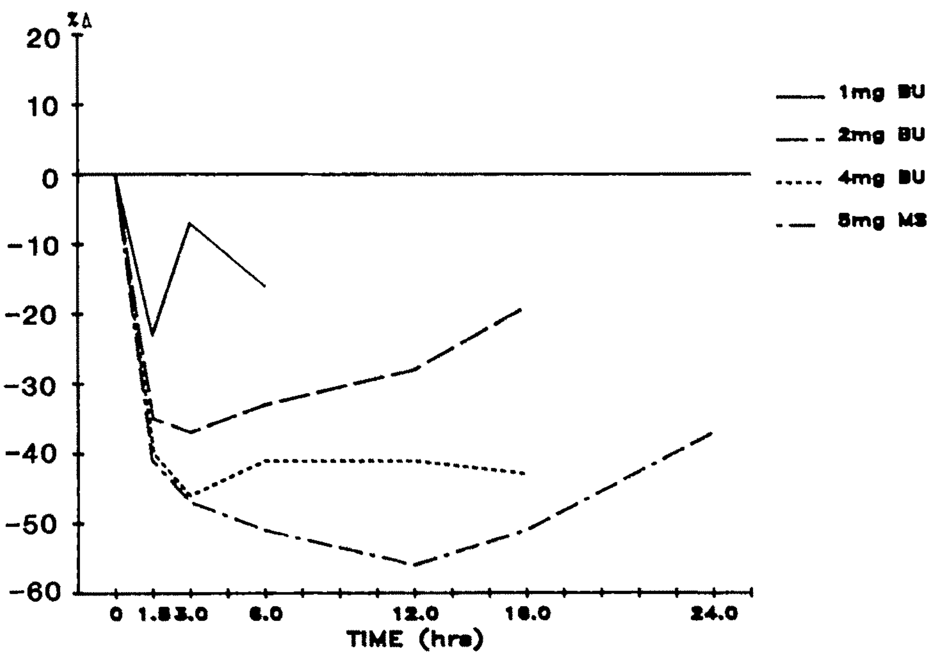

Figure 3. Percent change in $\dot{V}E_{50}$ at $PaCO_2$ 50 mm Hg from control values after patients received epidural injection of morphine or butorphanol.

seen in 8 patients given 1 mg butorphanol, in 10 patients given 2 mg and, in 17 patients given 4 mg. Analgesia was considered satisfactory when patient and observer assessment was 3+ to 5+. Patients gave both the morphine and the 4 mg butorphanol groups similarly high scores (Fig. 1). However, the observer reported 100% of patients given morphine as having satisfactory analgesia compared with 73% of patients given 4 mg of butorphanol ($P < 0.05$).

Table 3 shows time of onset and duration of pain relief after the second dose. Onset and duration of analgesia were similar after the first and second doses.

Carbon Dioxide Response Test

A complete set of CO_2 response curves were obtained in most patients. Figures 2 and 3 and Tables 4 and 5 show marked reduction in the CO_2 response slopes and $\dot{V}E_{50}$ from control values after the morphine and after 2 and 4 mg butorphanol, indicating a degree of central insensitivity to a rising CO_2 tension. They also show that the depression occurs as early as 1.5 hr and, with morphine, lasts up to 24 hr.

Table 6 summarizes data on the incidence of side effects, including pruritus, somnolence, nausea, vom-

Table 4. Minute Volume (L) with Pa_{CO_2} 50 Torr after Epidural Morphine or Butorphanol (Mean ± SEM), L/min

Time	Butorphanol, 1 mg	Butorphanol, 2 mg	Butorphanol, 4 mg	Morphine, 5 mg
Control	37.67 ± 2.85 (n = 30)	39.64 ± 2.76 (n = 29)	38.26 ± 2.52 (n = 30)	44.53 ± 4.09 (n = 31)
1.5 hr	27.70 ± 2.21* (n = 29)	25.80 ± 0.18* (n = 29)	21.40 ± 1.59* (n = 30)	26.28 ± 2.59* (n = 31)
3 hr	34.79 ± 3.92 (n = 21)	25.09 ± 1.90* (n = 21)	20.65 ± 1.21* (n = 26)	23.61 ± 2.94* (n = 28)
6 hr	31.69 ± 3.83 (n = 6)	26.71 ± 2.50* (n = 11)	22.55 ± 1.64* (n = 17)	20.40 ± 2.12* (n = 28)
12 hr		28.61 ± 3.13* (n = 5)	22.48 ± 4.18* (n = 5)	19.61 ± 1.78* (n = 28)
16 hr		32.28 ± 3.56 (n = 3)	21.87 ± 10.81 (n = 2)	21.63 ± 2.01* (n = 25)
24 hr				28.16 ± 2.65* (n = 21)

*$P < 0.05$; significant difference from control values.
Values are mean ± SEM.

Table 5. CO_2 Response Slopes After Epidural Morphine or Butorphanol (L/min·mm Hg^{-1})

Time	Butorphanol, 1 mg	Butorphanol, 2 mg	Butorphanol, 4 mg	Morphine, 5 mg
Control	1.96 ± 0.16 (n = 30)	1.97 ± 0.14 (n = 29)	2.06 ± 0.16 (n = 30)	2.37 ± 0.27 (n = 31)
1.5 hr	1.74 ± 0.15 (n = 29)	1.55 ± 0.11* (n = 29)	1.59 ± 0.11* (n = 30)	1.63 ± 0.16* (n = 31)
3 hr	2.08 ± 0.19 (n = 21)	1.52 ± 0.10* (n = 21)	1.49 ± 0.13* (n = 26)	1.55 ± 0.18* (n = 28)
6 hr	1.81 ± 0.19 (n = 6)	1.42 ± 0.08* (n = 11)	1.56 ± 0.17 (n = 17)	1.40 ± 0.14* (n = 28)
12 hr		1.49 ± 0.11* (n = 5)	1.17 ± 0.30 (n = 5)	1.16 ± 0.10* (n = 28)
16 hr		1.56 ± 0.07 (n = 3)	1.87 ± 1.48 (n = 2)	1.27 ± 0.14* (n = 25)
24 hr				1.66 ± 0.21 (n = 21)

*Significantly different from control values ($P < 0.05$).
Values are mean ± SEM.

Table 6. Percentage of Patients with Side Effects after Epidural Morphine or Butorphanol

Side effects	Morphine, 5 mg (n = 32)	Butorphanol, 4 mg (n = 30)	Butorphanol, 2 mg (n = 29)	Butorphanol, 1 mg (n = 31)
Pruritus	62.5*	0	0	0
Somnolence	21.9*	67.5	72.4	48.4
Nausea	6.3	3.5	0	0
Vomiting	3.1	0	0	0
Dizziness	0	3.5	3.4	0
Warm sensation	0	0	3.4	0
Blurred vision	0	3.5	0	0

*$P < 0.05$ for morphine compared with the butorphanol groups.

iting, and dizziness. Urinary retention could not be assessed because indwelling catheters in the urinary bladder were left in place for approximately 24 hr postoperatively. None of the patients had clinical evidence of respiratory depression (respiratory rate <10 breaths/min). Sixty-two percent of the patients who received morphine had pruritus, whereas none in the butorphanol groups had pruritus. Somnolence was

observed more frequently in patients given epidural butorphanol.

Discussion

The efficacy of epidural morphine in providing relief of postoperative pain is well established. Several studies have demonstrated that a single epidural administration of morphine produces prolonged analgesia without interfering with neuromuscular function or depression of the sympathetic nervous system (6–10). However, its use has been associated with the occurrence of undesirable side effects such as pruritus, nausea, vomiting, urinary retention, and respiratory depression (9–16).

One of the interesting findings of the present study is the paucity of side effects associated with epidural butorphanol. Side effects, especially pruritus, were markedly less frequent after epidural butorphanol than after epidural morphine. Epidural narcotic agonists such as morphine produce profound analgesia presumably by stimulation of μ-opiate receptors involved in the genesis not only of effective analgesia but also undesirable side effects such as pruritus, urinary retention, and respiratory depression. In addition, respiratory depression secondary to rostral spread of the poorly lipid-soluble morphine requires prolonged monitoring of the respiratory parameters. Stimulation of other spinal opiate receptors (κ) can also produce spinal analgesia, but with fewer side effects. Therefore, a drug such as butorphanol, a μ-agonist/antagonist and κ-agonist, also produces analgesia but is associated with fewer side effects. Its high lipid solubility and high affinity for opioid receptors are additional factors that contribute to the paucity of side effects with its use. High lipid solubility increases diffusion in the spinal cord and limits the amount of drugs remaining in the cerebrospinal fluid capable of reaching the brainstem, where side effects are detected (15).

Butorphanol was first introduced in 1978. It is a mixed narcotic agonist-antagonist and thus has low potential for abuse. Like nalbuphine, butorphanol is not a controlled substance. This is a major advantage that could make butorphanol of special value in long-term management of chronic pain.

There have been many studies (17–21) using highly sensitive methods of assessing respiratory effects of epidural opiates (e.g., CO_2 response curves and measurement of mouth occlusion pressures), but none of these studies have been done in the postcesarean section patients. Results from our study demonstrate that 5 mg morphine as well as 2 and 4 mg butorphanol injected epidurally are associated with a decreased central sensitivity to CO_2 as early as 1.5 hr after injection. The duration of depression is, however, shorter after butorphanol than after morphine.

In many centers, epidural morphine is avoided for treatment of postoperative pain because of the necessity of 24 to 36 hr respiratory surveillance (results from the present study confirm the necessity of patient monitoring for 24 hr). An agent providing 6–8 hr of pain relief, such as butorphanol in the present study, would be ideal, because patients could be kept in the recovery room for this time.

We conclude that 2 mg and 4 mg butorphanol administered epidurally in 10 ml saline solution is safe and effective in providing relief of post-cesarean section pain and is associated with only minor side effects. We recommend close observation for signs of respiratory depression during the period of analgesia.

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Special Article

Anesthesia for Spinal Decompression for Metastatic Disease

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Until recently, it has been widely believed that when patients with malignant disease develop neurologic symptoms due to spinal metastases progress of the condition is irreversible and surgery is futile. Thus, surgery of this type has been unusual, and the special problems associated with anesthesia for this heretofore relatively rare operative procedure have not been documented. However, because the contiguity of the Wellesley Hospital to the Ontario Cancer Institute enables a rapid consultation, smooth transport, and prompt surgery, approximately 250 patients with neurologic deterioration caused by spinal metastatic disease have undergone decompressive surgery at the Wellesley Hospital over the past 10 years.

These patients typically have had previous treatment for cancer, most commonly of the breast or prostate, have often been symptom-free for many years, and have gradually or suddenly developed back pain, paraparesis, or paraplegia, often with loss of sphincter control. Surgery may be indicated because of the rapid progression of symptoms in spite of radiotherapy, or because of encroachment by metastases on the vertebral structure, potentially with fracture-dislocation. Surgery involves spinal laminectomy with removal of the metastatic tissue compressing the spinal cord. Stabilization of the vertebral column with instrumentation, wiring, or prosthetic cement may be required, depending on the extent of skeletal destruction. Analysis of the first 150 cases performed at Wellesley Hospital showed that after surgery, 75% of patients had significant relief of pain, 66% became ambulatory, 16% had significant return of motor function, and 43% remained ambulatory and continent 6 months after surgery (1).

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Considering the potential benefits, surgical decompression as a means of preventing or reversing the neurologic deterioration of these patients may well become more widespread. The urgency and serious nature of the procedure, including the dangers involved in moving these patients, present potential pitfalls for the anesthetist. A review of our experience in managing these patients may be of help to the anesthetist faced with such cases, possibly at short notice.

Preoperative Assessment

Preoperative complications caused by metastases may include pulmonary atelectasis, pneumonia, or pleural effusion. Immobility due to pain or paralysis may predispose to pulmonary embolism. High thoracic or cervical lesions may impair intercostal or even diaphragmatic muscle power, with a threat of respiratory inadequacy (2,3). The latter is rare in our experience, presumably because, in contrast to traumatic cord injuries, the more gradual onset of neurologic deficit allows the patient to "learn" to use accessory muscles of respiration.

Involvement of the thoracolumbar sympathetic outflow may give rise to cardiovascular instability with the possibility, on the one hand, of orthostatic hypotension (4,5), or, on the other, of unusual susceptibility to fluid overloading, necessitating great care in balancing fluid replacement requirements (6).

Autonomic dysreflexia, especially with lesions above T-8, is also a potential problem. Patients with autonomic dysreflexia may have headache, palpitations, flushing, or pilomotor erection resulting from bladder distention or other visceral stimulation (7–9).

The musculoskeletal system must be examined carefully, with particular attention paid to the affected region of the spine, especially if the lesion is at the cervical level and if fracture dislocation is present. One should look also for the presence of silent me-

Table 1. Spinal Metastatic Disease Complications Relevant to Anesthesia

Caused by metastases	
Skeletal	Spinal instability due to pathological fracture
Neurologic	Intercostal or phrenic nerve dysfunction
	Autonomic dysfunction
Respiratory	Atelectasis
	Pneumonia
	Effusion
	Respiratory failure
Cardiovascular	Pulmonary embolism
	Unstable vasomotor tone
Hepatic dysfunction	Arrhythmias
Pain	Narcotic tolerance, addiction
Caused by radiotherapy	Vomiting, diarrhea, dehydration, hypovolemia
	Pulmonary pneumonitis, fibrosis
	Anemia
	Thrombocytopenia
	Immunosuppression

tastases at other levels in the spine, or in the limbs, which could sustain damage when the patient is being positioned on the operating table. At this time, a review of the patient's radiologic skeletal survey and a discussion with the surgeon are useful, especially with regard to the risk of cervical cord damage during endotracheal intubation. Other potential problems include elevation of plasma potassium and calcium levels secondary to tissue or bony destruction. Finally, many of these patients have severe pain, possibly of long duration, and will have become tolerant or addicted to narcotics.

Complications resulting from previous treatment, will, if present, usually be due to radiotherapy, which may cause nausea, vomiting, or diarrhea with the possibility of hypovolemia and electrolyte imbalance (8). Radiotherapy for thoracic lesions may result in a form of pneumonitis with hyaline alveolar exudate, associated early on with the potential for increased alveolar–arterial Po_2 gradient and later with fibrosis and restrictive pulmonary dysfunction (10). Recent wide-field radiotherapy may cause anemia, thrombocytopenia, and immunosuppression. Complications due to spinal metastatic disease and radiotherapy that may be relevant to subsequent anesthesia are listed in Table 1.

A history of previous chemotherapy is unusual in this group, but one must remain alert to this possibility. The dangers of anesthesia after certain forms of chemotherapy are well documented (11,12).

These patients are usually in the age range of 50–70 yr and so, in addition to the above considerations, they may be affected by the age-related degenerative diseases such as ischemic heart disease or chronic obstructive lung disease. They are often generally debilitated by the long course of their disease; marked protein loss (13), coupled with radiation-induced nausea, vomiting, or diarrhea, explain why many patients may present for surgery in a state of severe inanition.

Preoperative Preparation

Management of any of the above complications to optimize the patient's condition prior to anesthesia is in most cases obvious, but particular attention should be paid to improving the patient's volume status as much as possible in the time available. These patients are frequently very depressed and anxious, indeed devastated, by the sudden recurrence of a disease that they had believed cured, and that is manifesting itself in a way with particularly unpleasant implications in the lay person's mind. Therefore, in addition to arranging that adequate narcotics be made available to the patient during the preoperative fasting period, it is important to take time to reassure the patient in the most optimistic manner possible.

Choice of Anesthesia

Because the patient is going to be in the prone position for some 5–6 hr, regional anesthesia is contraindicated. When administering general anesthesia it is important to avoid any factor that may increase blood pressure or volume within the spinal canal. Thus, malposition of the patient, coughing, straining, hypercarbia, or hypoxia may make operating conditions difficult for the surgeon, and may dangerously increase blood loss.

Our standard practice is to induce anesthesia in a conventional manner with thiopental, followed by succinylcholine for tracheal intubation. Maintenance of anesthesia is with nitrous oxide supplemented by either a volatile anesthetic, such as isoflurane, or an intravenous narcotic, such as fentanyl, while relaxation is continued with pancuronium and respiration maintained by ventilator. As already indicated, tracheal intubation is a potential problem with cervical lesions, particularly when associated with an unstable fracture dislocation. In some cases it may be necessary to induce anesthesia and intubate the trachea with the patient on a Stryker frame with skull traction applied, or, where very unstable lesions are present, with the patient awake, and appropriately sedated, and after application of local anesthetic to the upper airway. Fiberoptic bronchoscopy may be necessary in some cases (Table 2).

Table 2. Anesthesia for Spinal Metastatic Surgery: Perioperative Complications in 117 Consecutive Cases

Preoperative	
Pneumonia or effusion	3
Cervical pathological fracture	15
Cervical pathological fracture requiring awake or fiberoptic tracheal intubation	7
Intraoperative	
Hypotension (<70 mm systolic) attributable to hemorrhage	12
Postoperative	
Patients with aggravated neurologic deficit postoperatively	
Cervical lesions	0
Thoracic or lumbar lesions	4
Respiratory inadequacy requiring ventilator assistance for >8 hr	4

In this type of surgery, hemorrhage is often sudden and massive; continuous and meticulous monitoring is thus of utmost importance. The majority of these patients are operated upon at the thoracic level (about 65%). Although surgery at the low thoracic or lumbar level allows the arms to be positioned above the head, and thus to be accessible for monitoring purposes, upper thoracic or cervical surgery demands that the arms be placed in an inaccessible position at the patient's sides. In these cases, it is essential that remotely placed monitoring and fluid replacement catheters be carefully positioned preoperatively in such a way that displacement, kinking, or pressure cannot affect them. Because of the long duration of surgery, with the potential for prolonged or sudden and massive blood loss, in all cases indwelling arterial and central venous catheters, and at least one, but preferably two, 16- or 14-gauge intravenous pathways should be inserted. Pulmonary artery catheterization may be indicated if cardiac dysfunction is suspected, as, for example, after doxorubicin (adriamycin) therapy (11). Although intraoperative monitoring of somatosensory evoked potentials may be helpful in the management of some of these cases (14,15), these facilities were not available at Wellesley Hospital at the time of writing. Accurate monitoring of blood loss is, of course, critical.

Correct positioning of these patients is necessary to prevent aggravation of cord damage, pathological fractures in the limbs, etc. Positioning is also important in ensuring optimal surgical access with a minimum of operative bleeding; it would be advantageous if these patients could be placed in the knee-chest position or prone in a McKay or Hall–Relton frame in which the paralysed abdomen is suspended most freely to promote a respiratory pattern with minimum mean intrathoracic pressure and free drainage of the vertebral venous plexus (16,17). However, the majority of patients have spinal lesions that are potentially unstable, and patients therefore are best positioned prone on a pair of longitudinal bolsters with an adequate gap between them to minimize pressure on the abdomen. When rolling the patient from the supine position onto the bolsters, great care must be taken to avoid flexion or extension that might aggravate the spinal lesion (Table 2). When it is known or suspected that spinal instability is present, the operation may have to take place with the patient on a Stryker frame. Once the patient is positioned, it is important to verify that the endotracheal tube remains correctly placed, that all monitoring and fluid replacement lines are functioning satisfactorily, and that pressure points are well protected. Because of the duration of the anesthesia there may be considerable heat loss, especially in patients with lesions at T-6 or above that may induce a poikilothermic state (18). Steps should therefore be taken to conserve body heat by use of a warming blanket, a low-flow system or humidification and warming of inspired gas, and by warming intravenously administered fluids.

During the operation it is important that muscle relaxation be well maintained, not only to control respiration and minimize hemorrhage, but also because, as in abdominal surgery, adequate relaxation of the long paraspinal extensor muscles is required for good surgical access.

Management of Blood Loss

Because of the prolonged nature of surgery and the large amounts of irrigation fluid often used in the operative site, assessment of blood loss is difficult. Accurate fluid replacement depends upon meticulous, ongoing weighing of sponges and measurement of suction losses with appropriate correction for irrigation fluid used, combined with continuous observation of pulse rate, arterial and central venous blood pressures, and urinary output. Deacock (19) states that during spinal decompression blood loss is "not heavy in uncomplicated cases and should be of the order of 200 ml only." This estimate agrees well with our own figures for blood loss during surgery for benign lumbar disc disease. However, in a recent review of 117 consecutive posterior spinal decompressions for metastatic disease carried out in this institution, average blood loss was dramatically greater than that incurred during decompressive surgery for benign disease, mean loss for surgery for metastatic disease being 2137 ± 1566 ml (the volume replaced by transfusion differing by a mean of 450 ± 480) (mean ± SD). In 12 of the cases with metastatic disease there

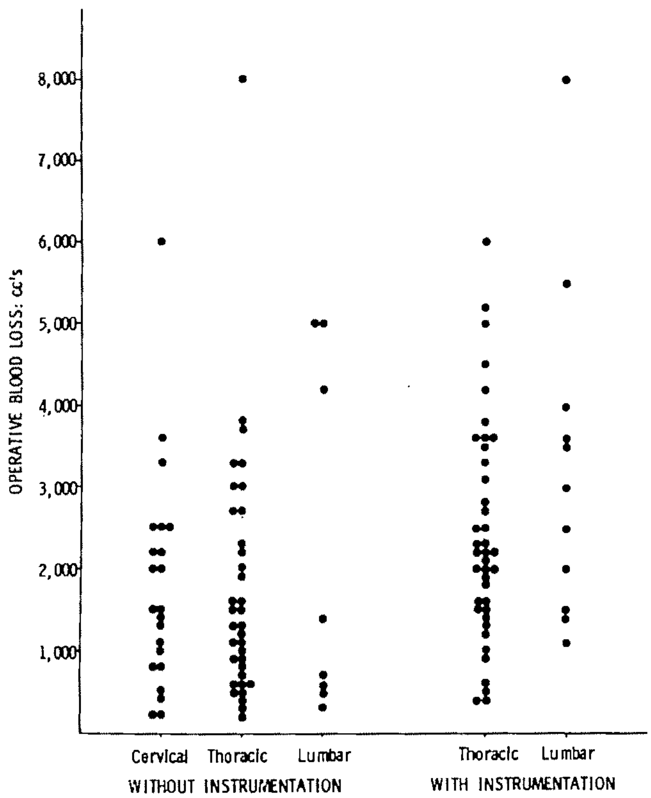

Figure 1. Scattergram showing blood loss measured during posterior decompressive laminectomy for metastatic disease.

was serious difficulty in keeping up with the blood loss using conventional transfusion techniques. Such major losses are attributable to the unusually hemorrhagic nature of metastatic deposits in bone where radiotherapy scarring may be present, and where local compression by tumor may cause venous engorgement, ligatures may not be applicable, diathermy may be of limited applicability, and bone wax applied to the friable bone surface tends to float off. The situation may be made worse if autonomic dysfunction due to cord damage impairs the patient's ability to compensate for blood loss (18). In addition, many of these cases proceed to instrumentation for stabilization (Harrington or Luque procedure) after decompression (Fig. 1), or an anterior approach may even be necessary, both of which may prolong the procedure by several hours, with inevitable increases in blood loss. A recent review of 14 consecutive cases of anterior decompression by the transthoracic approach performed at Wellesley Hospital showed a mean blood loss of 5557 ± 3737 ml, which is more than double the mean blood loss using the posterior approach.

Minimizing blood loss depends upon careful positioning of the patient to avoid venous congestion in the spinal canal, upon maintenance of normoxia and normocarbia, or possibly moderate hypocarbia, by paralysis and controlled ventilation, and upon adequate depression of reflex cardiac hyperactivity with volatile anesthetics or intravenous narcotics. It is tempting to use induced hypotension to minimize bleeding. Before doing so, one must take into account not only the usual contraindications, such as occlusive vascular disease affecting the heart, brain, or other vital organs, but also in spinal decompression it must be remembered that viability of the spinal cord is already endangered by compression with resulting local ischemia. To aggravate this by premature induction of hypotension may prejudice the changes of a satisfactory neurologic recovery (20). If induced hypotension is to be used to reduce blood loss, it should only be employed after the spinal cord has been satisfactorily decompressed. It should be remembered also that should "control" of hypotension be lost, resuscitation of a patient in the prone position is a formidable problem.

From the foregoing, it is obviously of the utmost importance in the management of these patients that facilities and assistance be available for the rapid transfusion of large amounts of warmed, filtered blood. At least 5 units of bank blood should be crossmatched and available preoperatively. Adequate and reliable intravenous access must be assured and one should be prepared to augment the stored red cell concentrate usually provided by blood bank with fresh blood components, including platelet concentrates. Re-use of the patient's own shed blood using "cell-saver" equipment is contraindicated because of the risk of dissemination of malignant cells (21).

Other Potential Problems

Theoretically, there exists a risk of increased muscle sensitivity to succinylcholine for a period of up to 18 months after the onset of motor neurologic deficits (22). Thus, the risk of incurring arrhythmias by succinylcholine administration must be balanced against the need for effective rapid sequence intubation in many of these urgent cases. Succinylcholine was in fact used in most of our cases, and no incidents attributable to its use occurred. The risk of intraoperative autonomic dysreflexia giving rise to hypertensive crises and cardiac arrhythmias has been mentioned above; no episodes attributable to the phenomenon were observed in this series. In cases where stabilization of the spine after decompression involves the use of methylmethacrylate cement, one must be on

the alert for a sudden decrease in blood pressure immediately after application of the polymer (23). Again, in this series, no episodes attributable to this were recorded.

Recovery

Postoperative respiratory inadequacy may be anticipated in patients with poor preoperative respiratory status caused by either chronic lung disease or the onset of neurorespiratory paralysis; respiratory distress syndrome could result also from massive volume replacement with intravenous crystalloid solutions. A degree of respiratory "splinting" may also be caused by extensive operative instrumentation to stabilize a particularly unstable spine. Postoperative respiratory insufficiency may in rare instances be due to succinylcholine administration when serum pseudocholinesterase levels are low in association with the patient's generalized disease (24), or where myasthenic syndrome complicates the underlying disease (22). In this series, only four patients required ventilatory assistance postoperatively (Table 2).

In conclusion, the material presented here, drawn from recent experience in managing an unusually large number of these potentially difficult cases, may be useful to the anesthetist faced with managing similar surgical procedures on short notice. These patients are often very ill, and require careful preoperative preparation. The ability of these patients to compensate for volume loss may be impaired, and, because a very large intraoperative blood loss may occur, the most important measures for the anesthetist must be the vigilant monitoring of blood loss and preparation for prompt, rapid, and massive blood replacement.

In summary, many perioperative complications confront the anesthesiologist anesthetizing patients for surgical decompression of the cord in spinal metastatic disease. The principal one is that of massive intraoperative blood loss. A retrospective review of the records of 117 consecutive operations carried out over a 3-yr period showed mean intraoperative blood loss to be 2137 ± 1566 ml (mean ± SD). Measures to minimize and compensate for blood loss of this magnitude are described.

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Clinical Reports

Hemodialysis during Cardiopulmonary Bypass: Report of Twelve Cases

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With the widened availability of support for the treatment of end-stage renal disease (ESRD), there are currently an estimated 72,000 patients maintained on chronic dialysis in the United States (1–3). Such patients appear to have an accelerated rate of development of atherosclerotic disease.(4) Fifty-five to sixty-five percent of the deaths in patients with ESRD are due to cardiac problems (5,6), most frequently bacterial endocarditis and myocardial infarction. Many of these patients will present for cardiac surgery. A number of reports of cardiac operations on dialysis-dependent patients have appeared in the past decade (7–9). Few have dealt with the problems that arise from the interaction of the anemia and the metabolic and body compositional disorders of renal failure, as well as the hemodilution, change in body compartment size, and use of potassium-containing cardioplegia solutions that are now features of cardiac operations with cardiopulmonary bypass (CPB) (10–12).

Ultrafiltration (10) has been used successfully in the management of the hypervolemia and anemia due to hemodilution in dialysis-dependent patients after open heart surgery, but is not capable of doing other than removing fluid. Scavenging of coronary sinus effluent (11) may control potassium but not water balance.

Intraoperative hemodialysis (HD) has also been reported (12). We now report twelve patients who were dialysis-dependent, who underwent open heart surgery, and in whom HD was used as an adjunct to management during bypass. To illustrate the potential indications for, and benefits of, this approach for some patients, two patients are described in detail.

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Patients

Ten of the 12 patients were maintained chronically on intermittent HD, and two on continuous ambulatory peritoneal dialysis (PD). On the evening before the operation, dialysis was attempted in all patients. Dialysis was well tolerated in eleven patients, but proved impossible in one patient (patient 2 below) on HD. The patients, the mode of dialysis, the type of operation, and preoperative and postoperative potassium and hematocrit (Hct) values are listed in Table 1.

Patient 1 (see Table 1) presented with ESRD and a history of coronary artery disease evidenced by one recent and one remote myocardial infarction, and coronary artery bypass grafting (CABG) undergone thirteen years earlier. He presented for operation with unstable angina and severe proximal coronary stenoses (90% left main and circumflex arteries, 100% right coronary artery). He was dialyzed uneventfully the evening before operation and presented for surgery with a normal serum potassium (4.0 mEq/L), an Hct of 19%, bleeding time of 6.5 min, prothrombin time of 13.9 sec (control, 11.5), and a partial thromboplastin time of 39.3 sec (control, 26.5).

Profuse intraoperative bleeding in this patient required the administration of 11 units of whole blood, 9 units of packed cells, 6 units of fresh frozen plasma, and 24 units of platelets as well as 800 ml of cardioplegia solution: in total, about 150 mEq of potassium. With the HD technique described, the serum potassium was readily maintained between 3.5 and 3.8 mEq/L during bypass, hypervolemia was avoided, and

'able 1. Description of Patients

'atient	Age	Etiology of nephropathy	Dialysis mode	Surgery	Hematocrit before/after CPB	Blood products transfused (units)	CPB K$^+$ (mEq/L)
1	69	Hereditary	PD	CABG	19/25	11 WB, 9 PC, 6 FFP, 24 Plts	4.0/3.5
2	49	Hypertension	HD	CABG	35/21	2 PC	6.1/4.3
3	33	Diabetes	HD	CABG	39/30	—	4.9/3.9
4	31	Nephrectomy	HD	AVR	25/28	2 WB, 3 PC, 4 FFP, 8 Plts	3.6/3.4
5	54	Lipoid nephrosis	HD	CABG	40/33	—	4.6/4.5
6	54	Nephritis	HD	CABG	29/20	2 PC	4.2/4.1
7	48	Nephritis	HD	CABG	22/27	5 PC	5.0/4.7
8	65	Analgesic-abuse	HD	CABG	26/25	4 WB, 3 PC, 2 FFP	4.3/3.9
9	47	Nephritis	HD	CABG	32/24	1 WB, 8 PC, 2 FFP	4.9/3.9
10	55	Nephritis	HD	AVR	29/27	2 PC	4.3/3.4
11	42	Nephritis	HD	CABG	34/30	2 PC	3.9/3.2
12	51	Diabetes	PD	CABG	34/33	2 PC	4.1/4.0

Abbreviations: PD, peritoneal dialysis; HD, hemodialysis; AVR, aortic valve replacement; CABG, Coronary artery bypass graft; CPB, Cardiopulmonary ypass; WB, whole blood; PC, packed cells; FFP, fresh frozen plasma; Plts, platelets.

target Hct of 25% was achieved. Patient 2, a 49-yr-ıld man with a history of ESRD and hypertension, ın HD for 4.5 yr, presented with unstable angina ıccurring at rest and with exertion, but with normal entricular function; i.e., a 70% ejection fraction and ıo signs and symptoms of dysfunction. Coronary ar-ery bypass grafting was proposed. Multiple attempts ıt HD on the evening before surgery were accom-panied on each occasion by severe angina, dyspnea, ınd marked hemodynamic deterioration, and failed o remove detectable amounts of either water or po-assium. Serum potassium levels remained elevated ıt 6.1 mEq/L on arrival in the operating room. Anes-hesia was uneventfully induced and maintained with 35 μg/kg fentanyl, 20 mg diazepam, 15 mg pancu-onium, and oxygen. Hemodialysis was begun im-nediately after the institution of CPB. Despite the use of the 44 mEq/L of potassium contained in the car-dioplegia, and the transfusion of 2 units of packed ed blood cells, intraoperative HD reduced the serum potassium to 4.3 mEq/L by the end of the procedure, ıs well as assuring a satisfactory reduction in BUN creatinine and water volume.

Methods

Anesthesia in these 12 patients consisted of diaze-pam, fentanyl, and pancuronium. Cardiopulmonary bypass was carried out using a Sarns modular pump and a bubble oxygenator (Cobe Optiflo II) primed with approximately 1100 ml of a balanced salt solution (Plasmalyte 148), 150 ml of 20% mannitol, 8000 units of beef lung heparin, and 500 ml of either dextran 40 or hydroxyethyl starch solution. After the establish-ment of bypass, the patients were systemically cooled to an esophageal temperature of 26–28°C. After aortic cross-clamping, a cardioplegic solution containing 26 mEq/L of potassium was injected into the aortic root in volumes of 700–1700 ml for myocardial protection.

After the induction of anesthesia and the institu-tion of CPB, the hemodialyzer was connected to the oxygenator circuit. Dialysis inflow was taken from the oxygenator coronary perfusion port. Blood after di-alysis was returned to the cardiotomy reservoir. He-modialysis employed a portable hemodialyzer (Drake-Willock 7200). Tap water was drawn from the oxy-genator water source and purified for use in the di-alysis bath by means of a reverse osmosis system (U-MARC 300-A) on the inflow line. A potassium-free hemodialysis bath concentrate (Diasol 34:120) was used to control serum potassium. Dialysate bath flow was 500 ml/min. A dialyzer blood flow of between 150–300 ml/min was used to maintain a serum potas-sium of approximately 4.0 mEq/L. Fluid removal to the degree necessary to maintain both a normal level in the oxygenator and a satisfactory hematocrit was effected by appropriate adjustment of the dialyzer transmembrane negative pressure within the range of 0–300 mm Hg.

Intraoperative HD using this approach has proved to be simple and free of complications, and is rou-tinely used as an adjunct to CPB in patients with ESRD. Hemodialysis was restarted uneventfully in all patients between 18 and 48 hr postoperatively.

Discussion

A number of other approaches have been successful in similar cardiac surgical patients with renal failure. These have included: 1) dialysis immediately before the operation followed by postoperative dialysis be-gun as soon as possible, and no other alterations in

perioperative management (7–9); 2) intraoperative scavenging of coronary sinus cardioplegia effluent (11); and 3) intraoperative hemofiltration, a commonly used technique to remove water by means of a Dow-Cordis Hemoconcentrator (10).

These alternative methods may not always be adequate. Unstable heart disease may make preoperative hemodialysis impossible, either because the urgency of the surgery does not allow adequate time for the dialysis, or because the stress of HD is associated with worsening symptoms or hemodynamic deterioration. This was the case with patient 2 in whom it was impossible to remove sufficient fluid or reduce the serum potassium below 6.1 mEq/L. Intraoperative HD was easily able to correct both of these problems.

Unanticipated hyperkalemia may also follow the use of large amounts of stored blood and blood products, as was the case in patient 1, and may also occur with prolonged periods of hypoperfusion, or severe anemia; in fact, any situation leading to metabolic acidosis. Five of our 12 patients were anemic, presenting in the operating room with a hematocrit of less than 30%, and eight required intraoperative transfusion to attain an average hematocrit of 25% after bypass.

No problems were observed resulting from dialysis-induced reduction of plasma drug levels in any patient. Although the plasma concentrations of anesthetic agents were not directly measured in these cases, no significant reductions in their levels would be expected to result from the intraoperative dialysis. Fentanyl, pancuronium, and diazepam all have relatively large volumes of distribution and exhibit greater than 50% plasma protein binding. Even assuming a high clearance ratio during hemodialysis, only a small fraction of the drug would be in the circulation at any time and thus available for removal by the dialyzer. Anesthetic drug supplementation was therefore not required and no patient had recall for intraoperative events.

Eight of the ten uncomplicated patients, despite a requirement for multiple transfusions, had a relatively stable intraoperative course and a good outcome, as did the other two who received no blood. All ten might have done as well with any of the previously described alternate methods. In the remaining two, however, the benefit from intraoperative HD was unequivocal because of situations in which either hemofiltration or coronary sinus cardioplegia scavenging would have been inadequate.

In summary, we have used intraoperative HD in 12 dialysis-dependent patients who required open heart surgery employing CPB. Hemodialysis was simple to initiate, could have been started at any time during CPB, and was effective in controlling metabolic and body compositional changes in two of the 12 patients when other methods would have been insufficient. We recommend its use during CPB in patients with renal failure when other methods have proven inadequate for the control of intraoperative fluid and electrolyte derangements, and note that it can be instituted at any time during the procedure.

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Cesarean Section under Epidural Analgesia in a Parturient with Mitral Valve Prolapse

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Mitral valve prolapse (MVP) is now considered a common cardiac valvular abnormality having been reported in up to 8% of healthy individuals (1). It is recognized most frequently in young women, but equally in both sexes in older age groups (1–4). Characteristic of this disease is a mitral valve with the structural abnormalities of elongated chordae tendineae and redundant valve leaflets (1,5). This results in a situation in which the leaflets prolapse back into the left atrium as the ventricle empties (6). The prolapse may or may not result in regurgitation depending on whether the leaflets coapt in mid- to late systole (7).

Regional analgesia necessitating a high level of sensory blockade is usually avoided in patients with MVP because the concomitant sympathetic denervation increases venous capacitance and decreases peripheral resistance. These two factors, by reducing ventricular volume, would be expected to increase the degree of prolapse and regurgitation.

We report the case of a patient with MVP who presented for emergency cesarean section and was successfully managed by lumbar epidural analgesia.

Case Report

A 27-yr-old woman with twin gestation at 29 weeks was scheduled for emergency abdominal delivery after failure of tocolysis with $MgSO_4$ (for premature labor). She had had a cough, sore throat, and fever for the previous 7 days, and was treated with ampicillin and gentamycin. Medical history included MVP and bronchial asthma. Mitral valve prolapse had been diagnosed 3 yr before by echocardiography, and occasional chest pain and palpitations had been treated with propranolol; for the past year she had been asymptomatic without medication. Her last asthmatic attack occurred 6 months previously.

The patient weighed 63.2 kg and was 157 cm tall. Blood pressure was 110/70 mm Hg; pulse was 100/min and temperature was 38°C. She had bibasilar rales but no wheezing on auscultation of the lungs. No cardiac murmurs or ejection clicks were heard. Her ECG revealed sinus tachycardia with about six unifocal premature ventricular ectopic beats per minute. Chest x-ray showed bilateral infiltrates and a normal-sized heart. Hematologic and electrolyte values were within normal limits. An arterial blood sample while breathing room air showed a pH of 7.48, a Pa_{CO_2} of 29 mm Hg, and a Pa_{O_2} of 69 mm Hg.

Central venous pressure, measured by right-sided, long-arm catheter, was 8 cm H_2O and increased to 10 cm H_2O after hydration with 1 L of lactated Ringer's solution. In the operating room, ECG and noninvasive BP monitors were applied and oxygen (6 L/min) administration by mask was started. With the patient in the right lateral decubitus position, the epidural space was identified by loss of resistance at the L3-4 interspace. Five 4-ml doses of 3% 2-chloroprocaine were injected through the needle over 12 min, while anesthetic level and blood pressure were determined frequently. After administration of 12 ml of the local anesthetic, the heart rate suddenly increased from 92/min to 120/min without concomitant hypotension. The tachycardia responded to two IV doses of 0.1 mg propranolol. A catheter was threaded into the epidural space and the patient turned supine with appropriate left uterine displacement. A T-6 level of anesthesia to pin-prick was obtained. A baby boy with Apgar scores of 4 and 6, at 1 and 5 min, respectively, and a baby girl with scores of 3 and 6 were born 7 and 8 min after skin incision. The mother's systolic pressure remained above 100 mm Hg and her heart rate between 90 and 98 beats/min without arrhythmias during the operation. Blood loss was minimal and was replaced with electrolyte solution; CVP remained between 10 and 11 cm H_2O. Thirty-five and 40 min after the initial epidural injections, two 5-ml injections of

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a mixture of 8 ml of 0.25% bupivacaine and 2 ml (100 μg) of fentanyl were administered through the epidural catheter, and the patient remained pain-free for the first 4 hr in the recovery room. Blood and sputum cultures revealed no growth; the pneumonitis resolved and the patient was discharged on the sixth postpartum day.

Discussion

MVP is often asymptomatic, although arrhythmias occur commonly. Review of 42 pregnancies in 25 women with MVP revealed no remarkable cardiac complications except for one episode of congestive heart failure in a patient treated for premature labor with a β-2-sympathomimetic drug (terbutaline); because of the potential circulatory side effects of this group of tocolytics, magnesium sulfate was used in our patient. Nevertheless, augmentation of the degree of prolapse must be avoided. Factors that augment the prolapse are those that result in a reduced ventricular volume, i.e., increased myocardial contractility, decreased preload, tachycardia, straining and excessive airway pressure. With diminished ventricular volume, the degree of prolapse of the leaflets into the atrium is accentuated; the smaller the left ventricle, the greater the prolapse (1). The anesthetic goals are therefore prevention of increased myocardial contractility and/or heart rate, maintenance of normal circulating blood volume, and avoidance of decreases in systemic vascular resistance or elevations in airway pressure (1,4).

Epidural analgesia was chosen for our patient despite the history of MVP because of the presence of pneumonia and bronchial asthma. The risk of hypotension and tachycardia consequent to high sympathetic blockade was recognized but preventive measures were taken and therapeutic measures were on hand. First, the obstetricians were asked to repair the uterus without exteriorization so that a sensory level to T-6 would suffice. Second, the local anesthetic was injected in fractional doses to permit development of compensatory mechanisms. Spinnato et al. (9) employed a similar technique, i.e., 2-ml increments of 3% 2-chloroprocaine (to maintain the sensory level at the eighth thoracic dermatome) for cesarean section in a patient with Eisenmenger's complex who developed minimal changes in heart rate and blood pressure. Third, the doses of local anesthetic were injected slowly to prevent excessive spread. Finally, preoperative expansion of intravascular volume guided by frequent BP and CVP measurements in addition to uterine displacement aided in maintaining hemodynamic stability.

Propranolol and a dilute phenylephrine solution were on hand for treatment of tachyarrythmia and hypotension. The advantage of both propranolol and phenylephrine, a vasopressor with predominantly α-agonist properties, lies in their negative chronotropic effect combined with lack of positive inotropic action. Although ephedrine with its β-agonist properties is the preferred vasopressor in prepartum women because of its beneficial effect on uteroplacental blood flow, it is avoided in patients with MVP as the resultant increase in heart rate and contractility may worsen the prolapse.

Antibiotics were administered not only for treatment of the pulmonary infection, but also as cardiac prophylaxis. Although antibiotics are not needed for routine vaginal delivery in women with heart disease, they are recommended for complicated deliveries (8).

In conclusion, epidural analgesia may be used safely and effectively for cesarean section in parturients with MVP if 1) the local anesthetic is administered in incremental doses and 2) dermatome level, volume status, and arterial pressure are monitored frequently.

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Spontaneous Respiration during Thoracotomy in a Patient with a Mediastinal Mass

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General anesthesia in the patient with a large mediastinal mass has been associated with life-threatening airway obstruction occurring after uneventful endotracheal intubation. Reports have described inability to maintain adequate air exchange with positive pressure ventilation, and acute airway obstruction occurring upon emergence and extubation (1–8). Some authors have recommended avoiding the use of muscle relaxants and positive pressure ventilation in order to preserve a normal transpulmonary pressure gradient and promote airway patency during spontaneous inspiration (1,3,8,9,10). Others have emphasized the importance of preoperative radiation therapy to reduce the extent of tumor encroachment before general anesthesia is administered (2,6,10).

We present a case of a patient with an anterior mediastinal mass and critical airway compromise who was allowed to maintain spontaneous ventilation throughout general anesthesia for a thoracotomy. Despite the risk of compromising the tissue diagnosis, the patient's management included preoperative radiation therapy to debulk the airway tumor. The mechanics of dynamic airflow in the presence of extrinsic airway compression are discussed, together with the implications for anesthetic management.

Case History

A 20-yr-old man was admitted as an emergency because of shortness of breath and tightness in his neck. He gave a 3-month history of increasing breathlessness especially when lying flat, difficulty in swallowing, a nonproductive cough, and a 5-kg weight loss, but denied fever, night sweats, pruritus, or adenopathy. One week prior to admission, he noted swelling of his face, neck, and shoulders that subsided spontaneously after 5 days. At that time he was diagnosed as suffering from pansinusitis, and was treated with an antibiotic and a bronchodilator, from which he obtained no relief.

On admission, the patient was anxious and in respiratory distress, with inspiratory and expiratory stridor. His face was plethoric, and there was marked anterior soft tissue swelling of his neck. Vital signs on admission included a blood pressure of 130/80 mm Hg, pulse rate of 90 beats/min, a respiratory rate of 30 breaths/min, and a temperature of 37°C. Further examination of the neck revealed no discrete adenopathy or thyroid enlargement. Auscultation of the chest demonstrated clear lung fields, but stridor was present during both inspiration and expiration; the expiratory phase was noticeably prolonged. Further physical examination was unremarkable.

A chest radiograph disclosed a large anterior mediastinal mass with compression of the trachea and both mainstem bronchi. Computed axial tomography demonstrated a critically narrowed (4-mm diameter) trachea from the level of the thoracic inlet to the proximal portions of the right and left mainstem bronchi. Arterial blood gas measurements with the patient breathing room air were pH 7.35, Pa_{CO_2} 49 mm Hg, and Pa_{O_2} 73 mm Hg. Laboratory data included a normal blood count and normal serum chemistries except for an elevated lactate dehydrogenase (LDH) of 1360 units (normal range 200–600).

Baseline spirometry and gas dilution lung volume measurements revealed moderate to severe obstructive airway disease with preservation of normal subdivisions of the lung volume. The flow-volume curve showed a plateau in both the inspiratory and expiratory phases, consistent with a fixed intrathoracic airway obstruction. The forced expiratory volume in 1 sec (FEV_1) was 2.02 L (45% of predicted), forced vital capacity (FVC) 4.09 L (72% of predicted), and there was significant reduction in small airway flow rates with forced expiratory flow (FEF_{25-75}) 1.67 L (27% of predicted).

In view of the patient's pronounced dyspnea and

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symptoms of superior vena caval obstruction, he underwent emergency radiation therapy, receiving a total dose of 600 rads to the mediastinum over three days. In addition, he received intravenous dexamethasone 10 mg q6h as prophylaxis for reactive edema of the tracheobronchial epithelium. His stridor resolved, and chest radiographs and tomograms demonstrated a patent tracheal lumen. Four days after admission, he was scheduled for an anterior thoracotomy (Chamberlain procedure) to obtain tissue for pathologic diagnosis.

One hour prior to operation, the patient was premedicated with intramuscular Innovar (2 ml). Anesthesia was induced with IV thiopental, 175 mg, and the patient was allowed to inhale 1–4% enflurane in a 1:1 mixture of nitrous oxide:oxygen. After the administration of lidocaine 100 mg IV, the trachea was intubated under direct vision with a 7.0-mm single-lumen endotracheal tube without difficulty and without the administration of muscle relaxants. The patient breathed spontaneously throughout the procedure, including the period during which the right hemithorax was open. Arterial blood gas tensions during spontaneous ventilation with the right lung collapsed on an FI_{O_2} of 0.8 were pH 7.25, Pa_{CO_2} 62 mm Hg, and Pa_{O_2} 256 mm Hg. No attempt was made to assume control of ventilation at this time since the patient's blood pressure, pulse rate and respiratory rate remained stable throughout. At the conclusion of surgery, he was extubated while still anesthetized and transferred to the intensive care unit. On arrival, he was agitated, complaining of pain and with moderate inspiratory stridor. However, his agitation and stridor resolved with the administration of IV morphine, 4 mg. The remainder of his postoperative course was uneventful. The mediastinal biopsy revealed non-Hodgkin's lymphoma, and he was referred to the oncology service for further treatment.

Discussion

This patient's severe respiratory distress on admission to the hospital raised concern that he might require emergency tracheal intubation and ventilatory support. However, as the patient's trachea and mainstem bronchi were compressed by tumor, the possibility existed that a standard endotracheal tube would not relieve the airway obstruction. Subsequent review of the literature revealed that a number of patients with large mediastinal masses had been intubated uneventfully but proved to be difficult to ventilate (1–6,8,11).

In 1975, Bittar (1) reported the case of a 16-yr-old patient with mediastinal Hodgkin's disease who was intubated with ease, but whose right hemithorax failed to expand with positive pressure ventilation, though no fault could be found with the tube placement or cuff. The obstruction to ventilation persisted until the operative procedure was abandoned and the patient was allowed to resume spontaneous respiration. The patient subsequently received radiation therapy to the cervical and mediastinal areas, and was anesthetized 2 weeks later without incident.

The anesthetic experience in 98 patients with mediastinal Hodgkin's disease was documented by Piro et al. (2). Among the patients (74/98) who did not receive radiation therapy before operation, five acute complications in airway management occurred. These included both difficulty in maintaining adequate gas exchange after intubation, and severe respiratory obstruction following emergence and extubation. In three of the five patients who experienced complications, there was no clinical evidence of airway compromise on preoperative evaluation. No difficulty with airway management was encountered in the patients (24/98) who underwent mediastinal radiation prior to surgery.

Under certain circumstances, it is possible to bypass an upper airway obstruction by stenting a longer endotracheal tube past the obstructed region (3). Bray and Fernandes (4) were able to pass a 4.5-mm bronchoscope in an 11-yr-old patient, and demonstrated severe anteroposterior compression of the trachea that was relieved by placing the patient in a right lateral semi-prone position. Todres et al. (5) were unable to maintain satisfactory ventilation in a 4-yr-old child with lymphoblastic lymphoma until one endotracheal tube was passed to the level of the carina, and a second smaller tube was passed through a tracheostomy into the left main bronchus. This arrangement was maintained until a course of radiation produced regression of the tumor.

Our patient did not require emergency intubation, but his extensive mediastinal mass placed him at high risk for complications during anesthesia. In addition to airway obstruction, case reports involving similar patients have described cardiac tamponade (6), acute superior vena cava syndrome (11), and obstruction to pulmonary artery flow (9–10) occurring after anesthetic induction. Biopsy under local anesthesia was proposed for our patient but was not feasible, because no superficial adenopathy was present. Despite the patient's acute symptoms, there was doubt whether immediate radiation was the best therapeutic choice, because radiation could destroy cellular architecture and interfere with a precise histopathologic diagnosis. However, the radiation therapists advised emergency radiation (confined to the central mediastinum) to re-

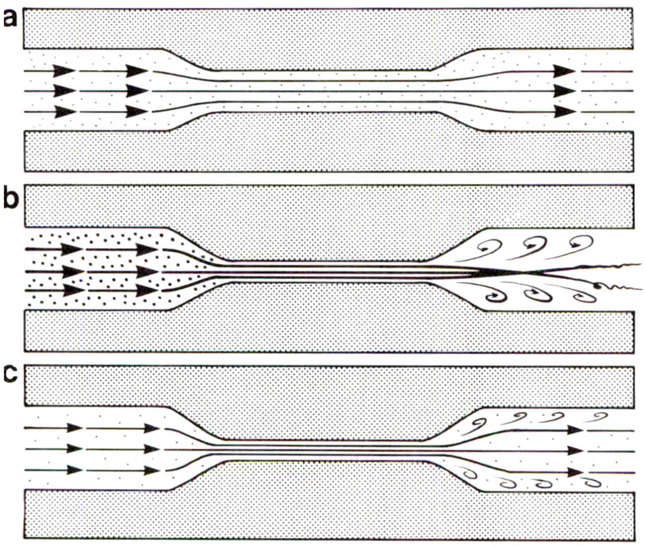

Figure 1. In noncritical stenosis **(a)**, the normal laminar flow profiles are compressed but resume their usual pattern distal to the stenosis. In critical stenosis **(b)**, laminar flow profiles are severely compressed. If the gas flow reaches critical velocity, flow will be disrupted into turbulent eddies, and laminar flow cannot be restored. With critical stenosis, if either the density or the velocity of the gas is reduced **(c)**, gas flow may be maintained with much less disruption of the laminar flow profiles.

lieve the patient's airway compromise and symptoms of superior vena cava syndrome. When a tissue specimen from the periphery of the tumor was obtained, it was diagnosed as non-Hodgkin's lymphoma.

It may be difficult to determine that radiation therapy is justifiable in the absence of a tissue diagnosis. However, the differential diagnosis of an individual patient's mediastinal lesion is limited, given the age of the patient, the clinical presentation, and the size and position of the mass within the chest. In this 20-yr-old patient, the presence of a diffuse, symptomatic mass in the anterior chest was considered by the oncologists to be presumptive evidence of a lymphoma. The chances are remote that any benign lesion will be of sufficient bulk to suggest a need for radiation or to cause life-threatening problems under anesthesia, although one case of a benign dermoid cyst has been described (9). The tumors that have been reported to cause either airway obstruction or hemodynamic compromise have been diffuse masses that enveloped vital mediastinal structures. The majority of these have been Hodgkin's lymphomas.

Although radiation therapy produced resolution of this patient's stridor and dyspnea within 2 days, it seemed prudent to maintain spontaneous ventilation and to avoid the use of muscle relaxants. During spontaenous inspiration, the normal transpulmonary pressure gradient distends the airways and helps to maintain their patency even in the presence of extrinsic compression. When this distending pressure gradient is abolished and the muscles of the chest wall and bronchi are relaxed, the weight of a mediastinal mass may provoke refractory airway obstruction. As this case demonstrates, spontaneous respiration may be maintained successfully even in the instance of an open hemithorax. Our patient developed a moderate respiratory acidosis, as expected, while spontaneously breathing enflurane at concentrations of 2% or higher. However, he experienced no arrhythmia, hypertension, or other sign of instability which might have compelled us to assist his ventilation.

While the benefits of spontaneous ventilation are clear, it is not as obvious why positive pressure ventilation has proved ineffective in some cases. The answer appears to lie in the fluid dynamics of Taylor dispersion (12), the process by which fluid or gas molecules moving through a tube under constant pressure will separate into a gradient of velocity profiles, with the fastest component in the center and the slowest components near the wall.

Gas flow can exist in one of two modes: 1) laminar flow, with fluid movements in parallel layers, or 2) turbulent flow, with turbulent eddies inhibiting laminar velocity profiles and randomizing the position of gas molecules across the tube. The transition from laminar to turbulent flow occurs when the gas reaches a certain critical velocity (13). When the cross-sectional area of a large airway is reduced, as with extrinsic compression by tumor, the average velocity of the gas must increase in order to maintain the same volume flow rate. At the higher velocity, gas flow within the compressed airway will be much more turbulent. If the stenosis of the airway is very abrupt (Fig. 1), complete separation of the normal flow profiles will occur and the jet stream at the center will constrict to a minimum value. Past the region of stenosis, gas flow is disrupted into turbulent eddies and cannot resume the laminar flow pattern needed for effective ventilation of the smaller, distal airways (14).

When difficulty with positive pressure ventilation occurs, the natural response of the anesthesiologist is to exert more pressure to generate a higher velocity of flow within the airways. For the patient whose large airways are compressed, this approach may prove disastrous, as flow becomes progressively more turbulent in the upper airways and less effective air exchange occurs downstream. Even passive exhalation may be impaired, and air trapping may result.

In some instances, patients with large mediastinal masses have tolerated the induction of general anes-

thesia and controlled ventilation without incident, and then have suffered airway obstruction upon emergence (2,8). This phenomenon may result from the excitation and pain that may often accompany emergence from anesthesia, leading to tachypnea and increased turbulence in the narrowed upper airways with a predictable loss of effective air exchange. The patient we describe did exhibit some agitation and stridor on emergence, which was relieved by a small dose of IV morphine. Anxiety, pain, or high sympathetic output should be avoided in such patients, because the maximal airflow they can generate is limited and tachypnea will compromise it further. For example, an awake intubation would be contraindicated, and any manipulation of the airway preferably should be performed under "deep" anesthesia.

In conclusion, this case demonstrates the importance of spontaneous respiration in the management of a general anesthetic in a patient with critical airway compromise from a mediastinal mass. Radiation therapy, despite the lack of a tissue diagnosis, was essential in this patient's preoperative management. The major goals of anesthetic care were to preserve spontaneous ventilation, to avoid the use of muscle relaxants or positive airway pressure, and to protect against noxious stimuli which might provoke tachypnea or cough and thus worsen the airflow dynamics.

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Anesthetic Considerations in Holoprosencephaly

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The holoprosencephalies are a series of teratologic malformations characterized by median deformities of the face and brain. The incidence is approximately one in every 13,000 births (1). Embryologically, there is a failure of the prechordal mesoderm. This mesoderm normally gives rise to the median facial bones and, by induction, influences the differentiation of the ectoderm as neural tissue, including its morphology.

Failure of the prosencephalon to undergo median cleavage results in a single-chambered ventricle, usually lacking olfactory bulbs and tracts. Other abnormalities include fused thalami, absent inferior frontal and temporal regions and a rudimentary isocortex (2).

Median facial abnormalities include hypotelorism in combination with a flat nose, and oral deformities such as a median cleft lip and palate. The nasal bones are either absent or hypoplastic.

There are no known previous reports of the anesthetic management of patients with holoprosencephaly. This report describes the various anatomic and physiologic problems that confront the anesthesiologist.

Case Report

A 7-month-old baby girl with holoprosencephaly required surgical correction of a cleft lip due to a failure to thrive. At birth she was noted to have microcephaly and multiple facial defects. These included hypotelorism, absence of the bridge of the nose and left nostril, and midline cleft lip and palates.

Computerized tomography showed enlarged occipital horns of the lateral ventricles and fused thalami. There was also absence of the frontal horns, third ventricle, and inter-hemispheric fissure anteriorly. Chromosomal studies were normal, indicating a 46 chromosome karyotype. No cardiac defects were noted.

Since birth the clinical course had been characterized by a failure to thrive, her weight increasing from 2900 to only 3500 g. Her temperature fluctuated between 36 and 39.5°C with no evidence of infection. Her heart rate varied from 110 to 180 beats/min.

Premedication consisted of 0.1 mg atropine intramuscularly 1.5 hr before surgery. An inhalation induction was performed using halothane, nitrous oxide, and oxygen. There was no difficulty with the airway, and maintenance anesthesia was administered by mask until intravenous access was secured and monitors applied.

Monitoring included lead II of the electrocardiogram, a precordial stethoscope, an oscillometric blood pressure device, a rectal temperature probe, and measurement of end-tidal carbon dioxide concentration (Capnoguard, Novametrix Medical Systems). Anesthesia was maintained with oxygen, nitrous oxide, and halothane. Tracheal intubation was performed using a Miller #1 blade and a 3.5-mm oral endotracheal tube. Four attempts were required before successful intubation was achieved, primarily due to the high arched palate and anterior larynx.

The intraoperative course was characterized by temperature fluctuations between 36.5 and 41.0°C, which required the use of surface cooling with a hypothermia blanket (Monotrol, Graymar Industries, Inc.) and ice packs. The baby's heart rate ranged from 150 to 200 beats/min and her blood pressure varied between 70/40 to 90/60 mm Hg. The end-tidal CO_2 was maintained in the range of 25–31 mm Hg. Attempts to obtain an arterial blood sample for measurement of gas tensions were not successful.

The remainder of the intraoperative course was uneventful. There were no signs of rigidity or cardiac dysrhythmias. After surgery the child was extubated and transferred to the pediatric intensive care unit, awake and crying.

Temperature instability continued to be a problem postoperatively, fluctuating between 36.5°C and 41°C and requiring cooling. During the first postoperative

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day, the patient had seizure activity on six occasions, each lasting less than 1 min. The seizures were finally controlled with diazepam and phenobarbital; however, she then became apneic and cyanotic, for which endotracheal intubation was done, followed by mechanical ventilation. With the exception of temperature fluctuations, vital signs remained stable and required no intervention.

At the end of the first postoperative day, the patient had a cardiac arrest from which she was resuscitated, but she remained comatose. Neurologic examination and electroencephalogram showed brain death.

Discussion

The cause of holoprosencephaly is unknown, but familial cases occur. Often there are associated maternal disorders such as diabetes mellitus, syphillis, toxoplasmosis, or cytomegalic inclusion disease (3). The prenatal history of this infant's mother was remarkable only for polysubstance abuse and a psychiatric illness treated with lithium and thorazine.

Two generic karyotypes exist, those with trisomy 13/15 (Patau syndrome or trisomy D) and those with a 46 chromosome karyotype. Patients with the 46 chromosone karyotype generally have fewer extracephalic abnormalities.

Neurologically these patients have poorly developed central nervous systems with severe mental retardation. In addition, there are temperature instability, seizures, and periods of apnea (2). Cardiac defects include dextrocardia and ventrical septal defects. Digestive system abnormalities are often seen and may include incomplete rotation of the colon and stenosis of the bile duct. Failure to thrive is common, and most infants die within the first year of life (4).

There are numerous potential problems in the anesthetic management of these patients. The first is that of airway management. The median facial and oral abnormalities may make use of an anesthetic mask and endotracheal intubation difficult. When confronted with such a patient, it would seem prudent to perform an awake tracheal intubation. In this case, even though tracheal intubation was difficult, it was possible to maintain a patent airway with a face mask.

Premedication of patients with holoprosencephaly using atropine has the beneficial effect of drying secretions and facilitating airway management. However, it can also induce tachycardia that can mask the early onset of malignant hyperthermia (5) or worsen the wide fluctuations of body temperature.

Due to airway and metabolic problems, it is important to utilize capnography and pulse oximetry and to measure arterial blood gas tensions as indicated by the clinical situation. The anesthesiologist must be prepared to deal with extremes of hyperthermia and hypothermia when administering anesthesia to these patients.

Patients with holoprosencephaly have been found by electrocephalography to have areas of the brain with repetitive seizure discharges and thus are usually receiving anticonvulsant medications. This patient was taking diazepam and phenobarbital to control her seizures. Her apneic episode was probably due to a combination of three factors: the anticonvulsant medications, emergence from anesthesia, and the inherent tendency toward apnea so often seen in these patients. This dictates the need for careful postoperative respiratory monitoring with tracheal intubation and controlled ventilation when in doubt. Because ketamine (6) and enflurane (7) both lower the threshhold for seizure-like activity, it is wise to avoid the use of these drugs in the anesthetic management of the patient.

Cardiac lesions are often associated with holoprosencephaly. This patient, however, had no demonstrable cardiac lesions, consistent with her 46 chromosomes. Nevertheless, each of these patients deserves a thorough cardiac evaluation for appropriate anesthetic management. The poor nutritional status and altered homeostatic mechanisms in these children also make it necessary to monitor them closely for the development of hypoglycemia. Biliary stenosis and hepatic malfunction also occur and must be considered in terms of drug metabolism as well as ability to maintain a euglycemic state.

In summary, a patient suffering from multiple congenital defects and physiologic derangements associated with holoprosencephaly is presented. Anesthetic management is complex, requiring particular attention to the altered function of the central nervous system and special monitoring to diagnose the cause of variations in temperature, respiratory patterns, and cardiac function.

The authors wish to thank Anita Guffin, MMS, and Joel A. Kaplan, MD, for their editorial assistance with this report.

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Pleural Effusion After CT-Guided Alcohol Celiac Plexus Block

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The accuracy and safety of an alcohol celiac plexus block have been substantially increased by the use of the computerized tomography (CT)-guided technique (1) because most of the complications and failures of a celiac plexus block with conventional radiologic control are closely related to the inappropriate placement of the needles (2,3). We have seen, however, two cases of pleural effusions after celiac plexus blocks with alcohol under CT guidance technique.

Case 1

A 49-yr-old woman was referred to us for relief of chronic back pain. A total gastrectomy had been performed for advanced gastric cancer 8 months earlier. Two months later she noticed increasing left back pain radiating to the left shoulder. A CT scan revealed retroperitoneal invasion by the cancer resulting in bilateral hydronephrosis. An alcohol celiac plexus block was indicated. It was performed under CT guidance using a posterior approach with a 9-cm, 21-g needle. Pain relief was obtained immediately after the injection of 5 ml of a mixture of 2% mepivacaine (Carbocaine) and 65% meglumine amidotrizoate (Angiografin). CT scan demonstrated the appropriate diffusion of the mixture in the left retroperitoneal fat tissue. Fifteen ml of a 90% alcohol solution mixed with metrizamide was injected 15 min later. The patient reported anterior chest pain on deep inspiration immediately after the injection. CT scans after the injection revealed the overflow of the alcohol solution from the retroperitoneal fat tissue to the left subdiaphragmatic area. Pleural effusion on the left side demonstrated by a chest roentgenogram in the lateral decubitus position on the following day (Fig. 1) was confirmed by a CT scan. Ascites was not seen on the CT scan. The CT value of the effusion was significantly lower than that of blood in the aorta, indicating that it was a serous pleural effusion. There was no fever or dyspnea. Aspiration of the pleural effusion was not attempted because there was no respiratory embarrassment and the pleural effusion showed no tendency to increase. The pleural effusion resolved after 2 weeks without treatment, as revealed by a CT and a chest roentgenogram in the decubitus position. Serum amylase levels were normal throughout. The patient had no recurrence of back pain in the 3 months since the block.

Case 2

A 40-yr-old man with advanced stomach cancer and left upper abdominal pain was referred to us for management of chronic pain. A celiac plexus block under CT guidance was performed with 15 ml of 90% alcohol solution mixed with metrizamide. A CT scan showed the diffusion of the mixture to the left subdiaphragmatic space. The upper abdominal pain was eliminated, but the patient reported a slight dull sensation in the anterior chest.

A CT scan and a chest roentgenogram in the decubitus view on the following day showed a collection of fluid in the left pleural cavity. The low CT value of the fluid suggested that it was serous in nature. The pleural effusion resolved after 3 weeks without thoracocentesis. Serum amylase levels were unchanged after the block.

Discussion

To our knowledge, fluid accumulation in the pleural cavity after a celiac plexus block under fluoroscopic or CT guidance has not been reported. Hemothorax is perhaps the most likely cause of fluid collection in the pleural cavity after a celiac plexus block secondary to small vessel oozing associated with puncture of diaphragmatic crus or pleura needle during the block. Though aspiration of fluid was not attempted, the low CT value of the fluid excluded this possibility in the present two cases, and suggested the serous nature of the fluid in both cases.

Pancreatitis may also cause serous pleural effusiòn.

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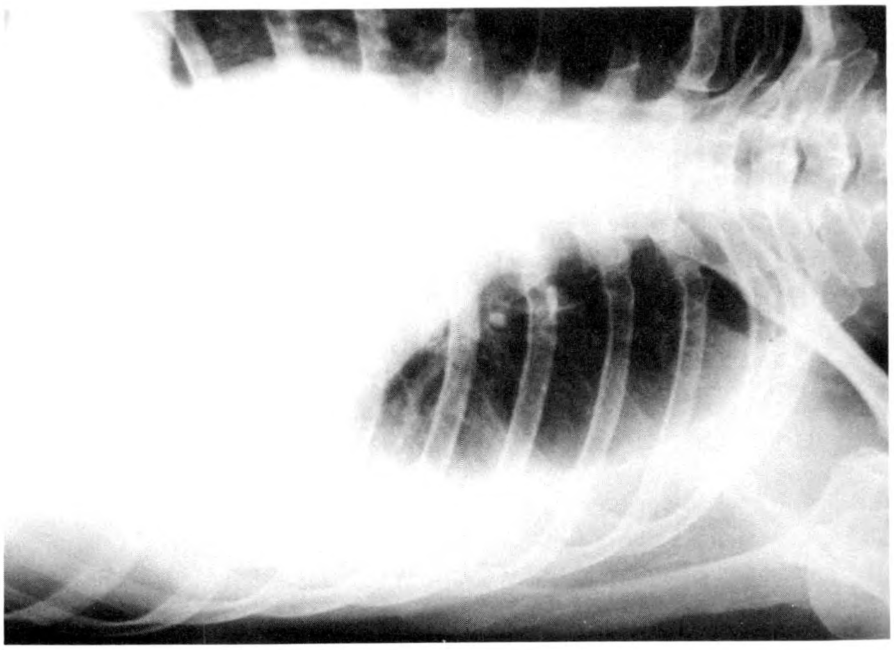

Figure 1. A chest roentgenogram in the left decubitus view on the day after the alcohol celiac plexus block showing fluid collection in the left pleural cavity.

Because alcohol was injected into the retroperitoneal space in which the pancreas also lies, it is theoretically possible that acute pancreatitis may develop after an alcohol celiac plexus block if the alcohol were to diffuse to the pancreas. The absence of intraabdominal fluid confirmed by CT scan and normal serum amylase values make it unlikely, however, that the pleural effusion was due to chemically induced acute pancreatitis in either case.

On the other hand, in both cases the spread of alcohol to the left subdiaphragmatic space was demonstrated on the CT image after injection of alcohol mixed with metrizamide. We thus assume this was responsible for the pleural effusion. Because the diaphragm is thin, the left hemidiaphragm, which was in contact with the alcohol, may have sustained severe chemical injury resulting in the exudation of sterile inflammatory fluid from the left diaphragm through the parietal pleura into the left pleural cavity. Anterior chest pain aggravated on inspiration (4) in Case 1 suggests inflammation of the lower parietal pleura. Moreover, the spontaneous disappearance of the pleural effusion after 2–3 weeks without fever or abdominal pain also suggests that the mechanism for the effusion was localized.

In summary, we reported two cases in which left pleural effusion developed after a CT-guided alcohol celiac plexus block, most likely related to the diffusion of alcohol to the left subdiaphragmatic space visualized by CT scan during the block. The pleural effusion resolved spontaneously without treatment within 2–3 weeks in both cases.

The blocks were done at Saiseikai Matsusaka General Hospital, 15-6 Asahi-cho, Matsusaka, Mie 515 Japan. We are indebted to Professor Craig Philipps for critical reviewing of the manuscript.

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Letters to the Editor

Prophylactic Epidural Blood Patch: The Controversy Continues

To the Editor:

We enjoyed the article by Baysinger et al. on treatment of dural puncture headaches after failed epidural blood patches (1). However, a prophylactic blood patch may have eliminated the need for the treatment required.

Controversy exists over whether or not an epidural blood patch should be done prophylactically after dural puncture with an epidural needle. A recent article by Quaynor and Corbey reported that a prophylactic blood patch instituted within 15 min of accidental dural puncture was effective in preventing headache in seven patients (2).

We wish to report a simple technique for doing a blood patch in patients given an epidural anesthetic after a dural puncture. We have had 11 lumbar punctures during placement of 1498 epidural anesthetics in pregnant patients during the past 12 months. Five patients developed postdural puncture headaches. Three of them were successfully treated with epidural blood patches within 24 hr of each occurrence. All five patients had uneventful epidural anesthetics after dural puncture. In the other six patients an epidural catheter was inserted one interspace above the puncture site and directed upward. Within 15–20 min after delivery, 15 ml of autologous blood were injected through the epidural catheters with the patients in a sitting position and the catheters subsequently removed. None of these six patients developed a headache. We feel that our results are more successful than those reported by Crawford (3) because of the blood volume that we injected.

Although the number of patients we treated is small, we feel that performing a blood patch through an epidural catheter is a simple and effective means of preventing a postspinal headache. It eliminates the need for another needle insertion and certainly warrants further investigation.

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Should Caffeine Become the First-Line Treatment for Postdural Puncture Headache?[1]

To the Editor:

Caffeine sodium benzoate (CSB) has been shown to be effective 70–75% of the time for the treatment of postdural puncture (PDP) headache in a controlled, double-blind study (1). Considering its simplicity, CSB compares favorably with the 90–95% effectiveness reported for epidural blood patch. Jarvis et al. (2) express bewilderment at the reluctance of the medical community to embrace CSB as a first line therapy for PDP headache. This reluctance may be based in part on the perception that CSB provides only symptomatic relief whereas EBP represents definitive (and therefore superior) therapy. There may also be a fear that if the PDP headache is allayed without definitively patching the dural hole, the patient may walk or sit upright and thereby cause more cerebrospinal fluid (CSF) leakage, possibly leading to more serious sequelae of CSF hypotension such as cranial nerve palsies.

However, these objections may not be justified. Postdural puncture headaches are postural; however, the rapid onset of the headache after assuming the upright position implies that whereas transfer of CSF through the foramen magnum is the major factor exacerbating the symptoms, increased leakage is not; the CSF must have already leaked out. Numerous studies have shown that enforced recumbency after lumbar puncture has no effect on the incidence of PDP headache (3–6). It is even possible that the upright position may improve the underlying pathophysiologic situation. When a needle is inserted into the subarachnoid space, the hydrostatic pressure of the CSF column will cause CSF to flow most rapidly through the needle when the patient is in the upright position. After the needle is removed, however, the situation becomes more complex because the CSF can no longer flow to the outside. This is illustrated schematically in Figure 1. The CSF column within the flexible dural sac is surrounded by the rigid spinal canal of bone and cartilage. In the upright position the dural sac may balloon out, approximating the hole to the spinal canal and possibly decreasing leakage. Figure 1 may be an oversimplification because there are semirigid structures within the spinal canal such as fat and blood vessels. The diameter

[1]The opinions or assertions contained herein are the private views of the author and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.

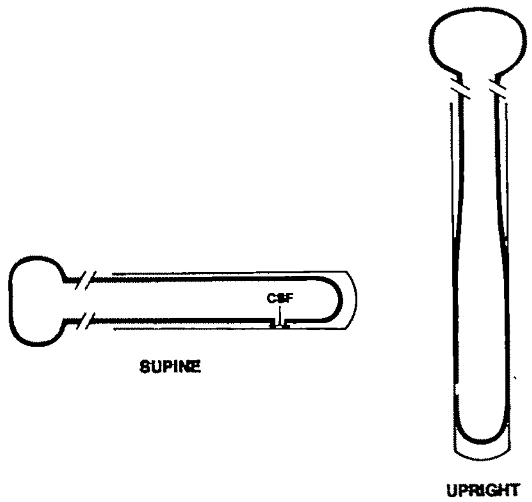

Figure 1. In the upright position the dural sac may balloon out approximating the dural hole to the rigid spinal canal and possibly decreasing leakage of CSF.

of the vessels may be further influenced by intrathoracic pressures, but there appears to be no a priori reason to assume that the upright position increases CSF leakage or necessarily increases the likelihood of cranial nerve palsy.

Is epidural blood patch really a definitive treatment? There is some in vitro evidence that blood injected epidurally adheres to the dura and may patch the hole (7). Two facts raise questions as to whether this is the major mechanism by which EBP relieves PDP headache. First, if adhesive patching were the primary mechanism, then prophylactic EBP should be quite successful, but it is not (8)! Second, when the epidural needle is placed at the same level as the initial lumbar puncture, then small volumes of blood (2–3 ml) should form an effective adhesive patch; however, much larger volumes (15–20 ml) are required to reliably alleviate the headache (9). The major mechanism of EBP may simply be filling of the spinal canal with gelatinous blood, thereby limiting the movement of CSF from the intracranial to the intraspinal space, which results in dilation of cerebral blood vessels and increased pain (10). Caffeine sodium benzoate appears to act directly to relieve the painful intracranial vascular distension.

In the past, PDP headaches have been treated by performing another lumbar puncture and injecting saline into the subarachnoid space. This is certainly symptomatic treatment. In fact, by making a second hole in the dura it should be the opposite of definitive therapy. Yet this treatment often permanently relieved the headache (11).

All of the various therapies for PDP headache may be symptomatic; thus, CSB prevents the painful dilation of intracranial blood vessels, whereas epidural blood (or saline) patching prevents this dilation by lessening movement of intraventricular CSF into the spinal subarachnoid space when the patient is in the upright position. Perhaps the major need is to break the pain cycle, thereby allowing the patient to ambulate.

The lack of enthusiasm for CSB in treatment of PDP headache is probably unjustified, but more experience is needed before these concerns can be permanently put to rest. Although Jarvis et al. may be overstating the dangers of EBP, EBP does require approximately a half-hour of the anesthesiologist's time and use of an epidural kit (about $30). Therefore, in many practice settings CSB may represent an effective, inexpensive, first line approach to the treatment of PDP headache.

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Preoperative Oral Fluids

To the Editor:

I was delighted by the appearance of yet more evidence (1) that the practice of prolonged preoperative starvation is neither justifiable nor humane. Permit me, however, to present three critical—if somewhat peripheral—comments.

May I plead that further reference to a volume of 25 ml of gastric contents as the "critical value" above which the subject is deemed to be "at risk," be promptly and permanently abandoned? This value is derived from two articles (which appeared in separate journals but which said roughly the same thing) by Roberts and Shirley (2,3). The estimate was an extrapolation from the results of experiments conducted on Rhesus monkeys: the experiments were to be described in a subsequent publication. That publication has not appeared. I fail totally to understand how one can assess the value of a technique of preoperative management by reference to a standard which is of highly du-

bious merit. Still less do I understand why a volume of gastric contents of 20 ml should pose significantly less hazard than one of say, 100 ml, provided that appropriate precautions to prevent the possible regurgitation of material into the pharynx are applied.

It was with somewhat cynical amusement that I noted that 6/59 (10%) of the patients who had received one of the much vaunted H_2-receptor blockers were found to have gastric contents with pH <2.5. That is surely an unacceptably poor level of precaution. When the far less expensive prophylactic use of magnesium trisilicate mixture is provided in the advised regimen, the incidence of failure is under 1% (4).

I am astonished that Maltby et al., when asserting that "Gastric emptying is delayed in late pregnancy," refer to an article by Van Thiel et al. (5). In the latter report there is not a single word concerning the rate of gastric emptying, the authors' concern being solely with the influence of pregnancy upon lower esophageal pressure and gastric reflux. There is indeed no reliable evidence that gastric motility is influenced directly by the progression of uncomplicated pregnancy up to the time of labor, and during the latter event, in the absence of hemorrhage and hypotension, the rate of gastric emptying is diminished only as a result of pain, apprehension, exhaustion, or narcotic analgesia.

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A Simple Method to Prevent Interference with Pulse Oximetry by Infrared Heating Lamps

To the Editor:

Prevention of hypothermia is a major goal in the anesthetic management of pediatric patients. Heating lamps help prevent radiant heat loss at times when an infant is uncovered, such as during induction, placement of monitoring devices, insertion of intravenous catheters and at the conclusion of the procedure when the surgical drapes are removed. Pulse oximetry is a noninvasive method of continuously monitoring arterial oxygen saturation (Sa_{O_2}) that has rapidly achieved widespread popularity (1). Unfortunately, infrared heat lamps interfere with pulse oximetry at the very times when knowledge of the arterial oxygen saturation

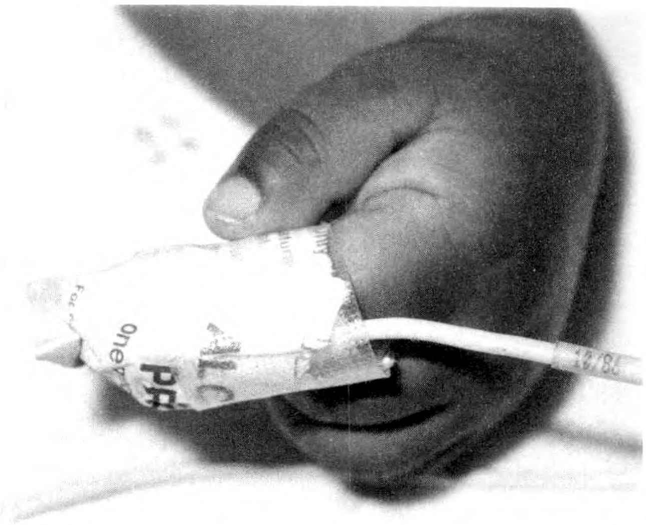

Figure 1. Aluminum foil packet from an alcohol wipe shown shielding the finger probe of the pulse oximeter.

(Sa_{O_2}) is most important. The high intensity of ambient light from the heat lamp prevents the photodetector from sensing light transmitted through tissue and calculating Sa_{O_2} (2). Whenever an infant or small child is anesthetized at our institution, a simple method is used to shield the finger probe utilizing the aluminum foil packet from an alcohol wipe. The packet is opened on one side and the alcohol wipe is removed. The empty packet is then placed over the tip of the digit with the probe on it and secured with tape (Fig. 1). The aluminum foil is nonporous, and effectively seals the finger probe from ambient light. Because the foil packet covers only one digit, the rest of the extremity remains available for placement of other monitors and insertion of intravascular catheters. In small infants in whom the probe is placed on the hand or foot rather than on a single digit, the foil packet is opened along three sides, wrapped around the entire hand or foot, and secured with tape. We find this method to be superior to other methods such as covering the extremity with a folded towel, which not only is bulky but precludes access to the extremity. This simple and convenient method of shielding the finger probe allows monitoring of arterial oxygen saturation at times when it is especially needed, as well as allowing for access to the extremity, without sacrificing the benefits of heating lamps when an infant or small child must be uncovered.

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Figure 1. Endotracheal tube impacting on arytenoid region.

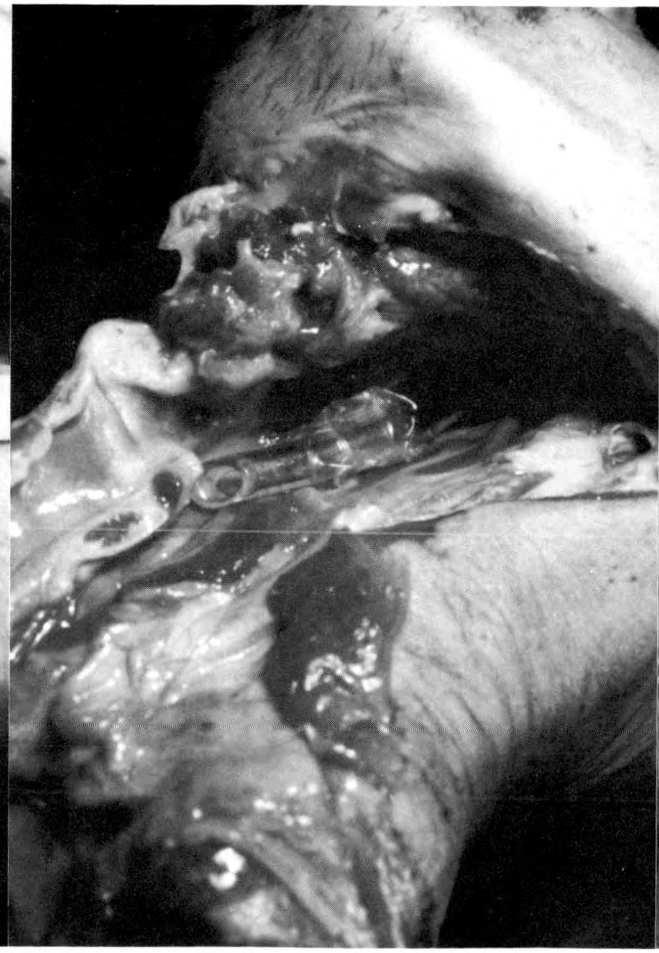

Figure 2. Endotracheal tube withdrawn.

Figure 3. Cuff inflated. Note change in relationship of tube tip with larynx.

Figure 4. Tube advanced, tip now lying at level of ventricle of larynx.

Figure 5. Cuff deflated and tube advanced into trachea.

Inflation of the Endotracheal Tube Cuff as an Aid to Blind Nasal Endotracheal Intubation

To the Editor:

We were recently confronted with the need for emergency awake tracheal intubation in a previously healthy 32-yr-old man who suffered bilateral hemothoraces in a motor vehicle accident. Blind nasal intubation attempts failed due to posterior passage of the tip of the endotracheal tube into the esophagus. Because cervical spine instability was likely, head positioning was contraindicated. Instead the endotracheal tube was advanced until breath sounds disappeared and then withdrawn one centimeter. The cuff was then inflated with 15 ml of air to elevate the tip of the tube away from the posterior wall of the pharynx and advanced 2 cm without loss of breath sounds. The cuff was deflated and advanced easily into the trachea.

Figures 1–5 demonstrate the sequence of events in a prosected specimen. In the presence of normal anatomy this technique is also likely to center the tip of the tube with respect to the lateral walls of the pharynx, although demonstration of this was not attempted in cadavers. It is also uncertain whether or not the tip-to-cuff distance is a major factor. The catheter used in this instance (8.0 mm inner diameter American Tracheal Tube, Mallinckrodt, Inc.) had a Murphy eye and the distance from the tip to the inflated cuff was approximately 2.5 cm.

Advantages of this technique are twofold: 1) no manipulation of the head and neck is necessary, and 2) no extra equipment is required.

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Contraindications to Electroconvulsive Therapy

To the Editor:

I would like to comment on the review article "Electroconvulsive Therapy and Anesthesia Considerations" recently published by Gaines and Rees (Anesth Analg 1986;65: 1345–56.). In an otherwise good review, these authors argue that there are 'absolute contraindications' to electroconvulsive therapy (Table 2, page 1348). Such an assertion is inconsistent with present practice, and its unchallenged statement in a journal as highly regarded as *Anesthesia and Analgesia* can only have a chilling effect on practice.

Convulsive therapy is a surgical therapy in psychiatry. It is often used in patients who are very ill, and for whom other therapies have either been unsuccessful, or their use associated with untoward effects. When treatment of the psychiatric condition is sufficiently compelling, as when patients are suicidal, debilitated, or starving, the 'absolute contraindications' are set aside and ECT has been considered a prudent intervention. Such interventions include treatment of patients with recent myocardial infarction, recent cerebrovascular accident, intracranial mass lesion, or cerebral vascular malformation. Some important articles and reviews are cited by the authors; some additional citations to the successful use of ECT in these conditions are appended.

Similarly, the litany of relative contraindications is to be challenged. Patients with the conditions cited may be considered high risk cases, and require special expertise on the part of therapists, but to label such cases as relative contraindications is not helpful. The prudent physician will not treat patients with these conditions with any therapy of any risk, unless the need is compelling. But when compelled, as by the absence of less riskful alternative interventions, CT has been given. At such times, the skill of the psychiatrist and that of the anesthesiologist, not societal prejudice, should determine the outcome.

Your readers should not be enjoined by the authors' injudicious injunctions against the use of an effective therapy.

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Current Anesthesia Practice for Electroconvulsive Therapy

To the Editor:

The importance of the participation of the anesthesiologist and good anesthesia practice to the success of electroconvulsive therapy (ECT) was stressed in the comprehensive review by Gaines and Rees (1). We recently sent out a questionnaire on ECT and current anesthesia practice to 152 institutions with residency programs. A total of 116 replied, of which 89 came from institutions where ECT is a form of therapy and 27 where ECT is not used. Some of the results are surprising.

The statement by Gaines and Rees that "It is now standard practice for the anesthesiologist to be consulted about the anesthetic management of patients undergoing ECT" (1) does not always seem to be the case. Two of the respondents stated that anesthesiologists were not consulted in the management of ECT patients at their institutions. Another two stated that only occasionally, when the psychiatrists felt that the patients' medical condition warranted it, did they participate. Three of 87 assigned the administration of the anesthetic for ECT patients to nurse anesthetists without the supervision of an anesthesiologist.

The conditions under which ECTs take place also do not seem to satisfy the anesthesiologists and in some cases appear to be substandard. In 18 institutions, multiple hospital sites for ECT were employed. In three, bedside ECT was the norm. Ten of the 87 respondents expressed a desire to change the usual location of ECT in their institutions from a room set aside for this purpose on the psychiatric ward to either the recovery room in nine cases or, in one case, to an operating room. The favored site for ECT (45 of 87) was the recovery room. In view of the frequency of cardiac dysrrhythmias associated with ECT, it was surprising that 13 of 87 respondents reported administering anesthesia for these procedures without the availability of a defibrillator. Four of 87 stated they did not monitor the ECG during ECT, though all reported monitoring the blood pressure. Twenty-four reported not having an anesthesia machine at hand, but utilized only an Ambu bag for oxygen administration.

Despite the known risks, a number of anesthesiologists (49 of 87 respondents) agree with the report of El Ganzouri et al. (2) and either discount totally or, in the light of psychiatric illness, accept the risks of administering anesthetics without cessation of monoamine oxidase inhibitors. In addition, 27 of 87 agree with Wyant and MacDonald (3) and do not routinely pretreat patients either intramuscularly or intravenously with an anticholinergic agent in anticipation of a bradyarrhythmia.

The above questionnaire, the results of which are only partially reported here, represents only a sampling of the many institutions in which ECT is used. In some cases, however, the results suggest less than optimal anesthetic care, where anesthesiologists are not consulted, and a willingness on the part of some anesthesiologists to compro-

mise aspects of care for ECT patients, taking risks that for other patients would not likely be entertained.

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Cannulation of an AV Fistula as a Cause of Falsely Low Oxygen Tension during Anesthesia

To the Editor:

We recently encountered a case in which an unexpectedly low arterial oxygen tension was reported during anesthesia. The cause was found to be due to the fact that the sample was obtained in the presence of an arteriovenous fistula. It was revealed by angiography and blood gas measurement during surgery. Although many causes of low oxygen tension during anesthesia are well documented, the cause of our case deserves mention because of its rarity.

A 58-yr-old man who had undergone surgical resection for bronchogenic carcinoma three years earlier was scheduled for resection for a metastatic brain tumor. After induction of anesthesia with thiamylal, 6 mg pancuronium were given for tracheal intubation. Anesthesia was maintained with 1.5% enflurane and 66% nitrous oxide in oxygen. A left radial artery cannulation for blood sampling was smoothly performed with a 20-gauge catheter. Blood refluxed into the catheter in pulsatile fashion.

Thirty minutes after induction, the first blood gas analysis showed a pH of 7.48, a Pa_{CO_2} of 23 mm Hg, and a Pa_{O_2} of 109 mm Hg. The inspired oxygen concentration was increased to 50%. One hour later the second showed a Pa_{O_2} of 106 mm Hg. The FI_{O_2} was increased to 1.0. Twenty minutes later the pH was 7.47, the Pa_{CO_2} 31 mm Hg, and the Pa_{O_2} 72 mm Hg. The patient's blood pressure at that time was 130/80 mm Hg with a regular pulse of 75 beats/min. Clear respiratory sounds were heard bilaterally. Blood in the operative fields was not dark. An arterial blood sample was taken from the dorsalis pedis artery with an FI_{O_2} of 1.0. The Pa_{O_2} was 568 mm Hg. The inspired oxygen concentration was then returned to 33%.

Two procedures were carried out during surgery to define the cause of this discrepancy in Pa_{O_2} values. First, an-

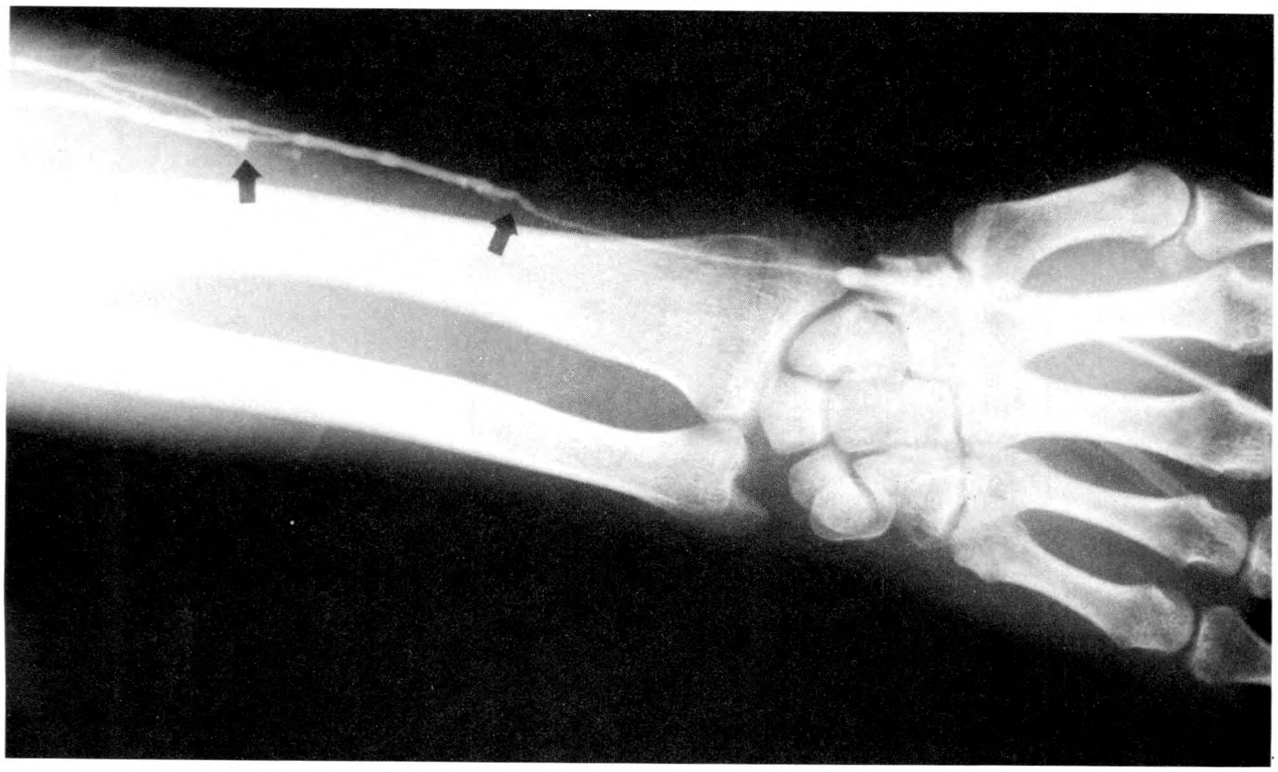

Figure 1. Angiogram showing the occlusion of the radial artery (left arrow) and the arteriovenous anastomosis in the radial part of left forearm. Right arrow indicates the tip of the catheter in the vessel.

giography was performed with an injection of contrast medium through the radial catheter. This demonstrated that the radial artery was occluded, that there was an arteriovenous anastomosis in the radial part of the left forearm, and that the tip of the catheter lay in a vessel connected to the anastomosis (Fig. 1). Second, blood gas tensions measured in samples simultaneously collected from the radial catheter, the dorsalis pedis artery, and a peripheral vein of the left arm with an $F_{I_{O_2}}$ of 0.33 had Pa_{O_2} levels of 71, 199, and 42 mm Hg, respectively.

It was therefore concluded that the unexpectedly low oxygen tension of the samples from the radial catheter was caused by an arteriovenous admixture due to an arteriovenous anastomosis.

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"Training" of Pediatric Endotracheal Tubes

To the Editor:

In pediatric patients the larynx lies so far anterior that insertion of an endotracheal tube frequently requires a stylet to provide the curvature needed for intubation. I wish to describe a simple technique that makes the pediatric tube properly curved without use of a stylet. I insert the tip of the endotracheal tube (Fig. 1A) into the tube connector (Fig. 1B) and keep it there until I am ready for intubation. When the tip of the endotracheal tube is removed from the connector, the tube maintains proper curvature as shown in Figure 1C. This simple manipulation of the tube has proven very effective and eliminates the possible complications from use of a stylet. Adult endotracheal tubes can also be "trained" in an identical fashion.

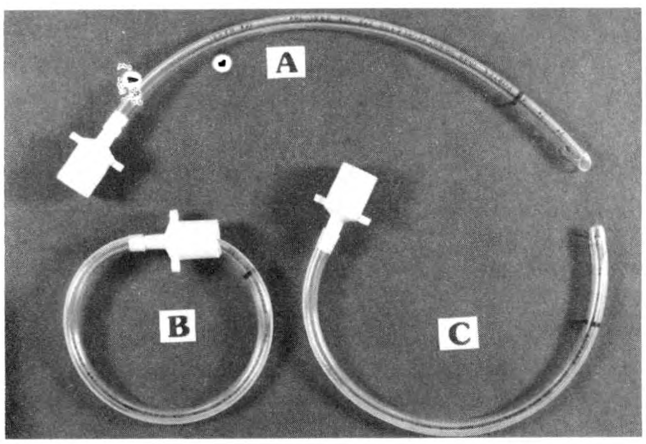

Figure 1. Pediatric endotracheal tubes. A, Before being trained; B, being trained; C, after being trained.

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The Kirschner Wire as a Readily Available Tunneling Device for the Placement of Subcutaneous Intraspinal Narcotic Delivery Systems

To the Editor:

The use of intraspinal narcotics to relieve pain of malignant origin represents a great advance in cancer pain management. For patients with more than a short life expectancy, implantation of subcutaneous delivery systems have been advocated to avoid complications including infection and catheter breakage (1–4).

We have had difficulty in obtaining tunneling devices when we wish to implant subcutaneously tunneled catheters or reservoirs at the various community hospitals at which we provide pain management services. We have circumvented this problem by using a Kirschner (K) wire that is available in even the smallest community hospitals. We have found that the 0.45-mm K-wire will fit most commonly utilized implantable catheters including the Infusaide Intraspinal Kit and Groshong Catheter. The wires are malleable, which allows them to be shaped to the contour of the patient's flank. After using the wire, it can be resterilized and used again.

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Pseudocholinesterase and Affective Disorders

To the Editor:

Pseudocholinesterase and other cholinesterases play an important role in the hydrolysis of drugs (succinylcholine, ester local anesthetics) that may be administered by the anesthesiologist. In addition, pseudocholinesterase plays a role in maintenance of the blood brain barrier, and acetylcholinesterase is important in modulation of neural and neuromuscular transmission. In this regard there are a number of studies in the psychiatric literature that correlate abnormal cholinesterase levels with affective disorders (1–3). This association has not been described in the anesthesia literature.

Recently we anesthetized a 15-yr-old 51-kg girl with a family history of affective disorders who experienced prolonged neuromuscular blockade after administration of succinylcholine due, in retrospect, to the presence of atypical pseudocholinesterase (dibucaine number 21 and 14 on two determinations). The patient's medical problems (abdominal pain) were considered to be functional as no organic cause was detected at endoscopy. The patient's 22-yr-old brother is institutionalized for treatment of schizophrenia.

Our patient with atypical pseudocholinesterase, a functional gastrointestinal disorder, and a brother with affective disorder introduces the question of whether the anesthesiologist should suspect the presence of atypical pseudocholinesterase in families with psychiatric disorders. Indeed, low pseudocholinesterase levels and atypical pseudocholinesterase have been found in schizophrenic patients (4). Pseudocholinesterase abnormalities and low levels of red cell acetylcholinesterase may reflect changes in central cholinergic transmission, resulting in affective disorders (5). We believe that a preoperative history of affective disorders in patients or family members should alert the anesthesiologist to the possible presence of atypical pseudocholinesterase.

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Pericardial and Subcutaneous Air after Maxillary Surgery

To the Editor:

Drs. Sanford et al. have published a valuable article describing potential adverse sequelae secondary to positive pressure ventilation associated with anesthesia and surgery on the hard and soft tissues of the head and neck (1).

In the literature of the specialty, pericardial and mediastinal air are well recognized complications of oral and maxillofacial procedures and may not be as infrequent as the authors suggest (2,3). Perhaps many instances are not diagnosed because the amount of air involved is slight or because of spontaneous resorption. However, fatalities associated with maxillofacial surgery may occur even without cardiovascular compromise when air in the mediastinum carries with it bacteria from odontogenic infections (4).

Sanford et al. did not mention what surgical instrumentation was used for access to the maxillary sinus. Positive pressure ventilation may in fact not be the cause of the appearance of air in cervical or mediastinal fascial planes, particularly if pneumatic handpieces have been used during facial skeletal surgery (5). Gas driven handpieces alone can lead to dramatic emphysema in a matter of seconds and positive pressure ventilation when the patient is being masked during emergence can be expected to predictably force air into potentially susceptible fascial planes opened by surgery or other means. Unfortunately, limiting the use of the mask to deliver positive pressure does not eliminate the need for monitoring because similar pathology has been reported even with spontaneous ventilation (6). Emergency measures may be necessary if severe pneumomediastinum compromises the patient's cardiovascular function.

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Another Case of Probable Seizure after Sufentanil

To the Editor:

We read with interest the letter by Molbegott et al. (1) describing seizurelike activity in two patients after sufentanil administration. We would like to report a similar case that occurred recently at our institution.

An 86-yr-old man weighing 60 kg was scheduled for left hip pinning after a fractured femur. He denied any significant neurological or medical history and denied taking medications of any kind. A preoperative arterial blood sample, obtained while breathing room air, had a pH of 7.38, a P_{CO_2} of 33 mm Hg, and a P_{O_2} of 73 mm Hg. He received no premedication. After 3 min of preoxygenation, vecuronium 1 mg was given intravenously, immediately followed by sufentanil, 100 μg. One minute later the patient became unconscious, and developed tonic-clonic movements in all extremities. Succinylcholine, 100 mg IV, was administered and the trachea was intubated after ventilation with O_2. Tonic-clonic movements subsided after succinylcholine and did not reccur after recovery from neuromuscular blockade. Anesthesia was maintained with 1% isoflurane in O_2. The intraoperative and postoperative course was uneventful. Neurologic examination 12 hr after recovery from anesthesia was unremarkable. Electroencephalogram and CT scan 1 week later did not show any abnormalities.

Molbegott et al. (1), reported convulsions after sufentanil in two patients. One convulsed after 40 μg, the other after 60 μg. Our patient developed what appeared to be a generalized seizure almost immediately after injection of 100 μg of sufentanil without evidence of hypoxia or changes in vital signs and with a normal neurologic and drug history. Although one of Molbegott's patients had Parkinson's disease and the other received 10 mg metoclopramide daily for a rather long period of time, our patient had no apparent CNS dopamine depletion nor had taken any drugs at all.

Convulsions have been demonstrated in dogs undergoing high-dose sufentanil anesthesia. Factors that modify the convulsion threshold of narcotics include the speed of intravenous injection, metabolic disturbances, and drug combinations (2). Experimental findings (2) together with the two cases reported by Molbegott et al. (1) and the present case suggest that generalized convulsions can occur after administration of sufentanil. As the three patients were 79, 67, and 80 yr old, age may also play a role in the convulsive threshold of sufentanil.

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Book Reviews

Clinical Application of Respiratory Care, 3rd Edition

Barry A. Shapiro, Ronald A. Harrison, Robert M. Kacmarek, and Roy D. Cane. Chicago: Year Book Medical Publishers, 1985, 613 pp.

This book attempts, as the authors state, "to coalesce the known technology and science into a conceptual and non-technical perspective that can be utilized by all personnel involved in respiratory care." A gigantic task, and one which they come very close to accomplishing.

The text is divided into eight sections beginning with a very basic review of the functional anatomy of the pulmonary system and leading to its clinical evaluation. These four chapters (and indeed the entire text) are clearly presented and well written and obviously designed for the novice student. At times, the explanations are almost painfully simple, for example, "when a photographic film is exposed to x-rays it turns black."

The editors have elected to use some different approaches in that each succeeding section builds on the previous sections. Thus, the reader can use the text as a progressive course in respiratory care. The advantage of this is that there is a natural sequence to the chapters and sections. However, the disadvantage, at least for the student, is that each successive chapter assumes the knowledge contained in all the previous chapters, making this book difficult to use as a reference text.

Despite this shortcoming, the book is highly recommended for students in any respiratory care program. It will also benefit any respiratory technicians who need to review updated material. It would also serve very nicely for physician-directors of respiratory care units as a basis for a teaching program. For the general anesthesiologist, I'm afraid it would be of little help.

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Diagnostic Methods in Critical Care, Automated Data Collection and Interpretation

William C. Shoemaker and Edward Abraham, eds. New York: Marcel Dekker, 1987, 528 pp, $69.75.

Presenting volume 9 of the *Basic and Clinical Cardiology* series, the editors state, "The aim of this volume is to provide information about the diagnostic modalities available in the critical care unit and also to apply data produced by these diagnostic procedures to improve care of the critically ill patient." Twenty-three authors have contributed 15 chapters, which cover several widely used technologies (e.g., cardiac dysrhythmia monitoring), emerging technologies (e.g., cardiac positron emission computed tomography and magnetic resonance imaging), and applications to specific clinical problems (e.g., AIDS and septic shock).

Despite the title of the volume, the minority of the chapters deal with automated data collection and interpretation. The chapters are individual essays which are not tied together and easily could be read in any order. Established investigators have contributed several excellent reviews of emerging technologies such as transcutaneous P_{O_2} measurement and computer applications to clinical pharmacokinetics. These chapters inevitably reflect the personal experiences and biases of the authors, and many useful insights and concepts are presented. Some information is presented redundantly as in the chapters titled "Transcutaneous P_{O_2} Measurement" and "Clinical Application of Noninvasive Tissue Oxygen Monitoring." Nonetheless, the overall readability of the volume is not diminished by this redundancy.

Chapters covering common monitoring methods such as those for cardiac dysrhythmias and respiratory function present material which has been discussed in a number of anesthesia and critical care volumes, and it is doubtful that many readers will find these chapters of new and unusual value. Anyone interested in acquiring physiologic data for clinical or laboratory research with no previous experience in this area will find the chapter "Real-Time Data Acquisition and Control" to be invaluable. A careful overview of the issues associated with real-time data acquisition is buttressed with a wealth of practical information including details such as manufacturers' addresses and telephone numbers.

Overall, this volume may be viewed as a collection of opics. It is valuable to the extent that these topics are of ndividual interest. The book is not comprehensive. For xample, 64 pages are devoted to application of the Clark lectrode technology, whereas pulse oximetry is covered in wo paragraphs. With these limitations in mind, many cliicians will find this volume worthwhile and pleasant reading.

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Muscle Relaxants: Side Effects and a Rational Approach to Selection

saac Azar, ed. New York: Marcel Dekker, 1987, 238 pp, $83.50.

This book, the seventh in a series on the subject of clinical pharmacology under the general editorship of Murray Weiner, contains chapters contributed by various authors.

The first chapter, on the autonomic effects of neuromuscular blocking agents, covers the general field of autonomic pharmacology in a very lucid fashion as it applies to neuromuscular blocking agents. For those unfamiliar with he concept, "autonomic margin of safety" is presented very clearly. In the second chapter, another complication of muscle relaxants, histamine release, is covered. This chapter brings out two important points, namely: 1) maximal histamine release can be markedly reduced by slow injection of the drug, and 2) a similar reduction can be obtained by prophylaxis with H_1 and H_2 histamine blockers.

In the chapter on the use of muscle relaxants in patients with neuromuscular disease, the concise description of the regional curare test for the diagnosis of myasthenia gravis is appreciated. The only serious disagreement this reviewer has with the text concerns the mechanisms responsible for the development of contracture in denervated muscle. In the reviewer's opinion, it has been reasonably well demonstrated that after denervation, white skeletal muscle takes on many of the characteristics of red muscle, resulting in the development of contracture with exposure to a cholinergic agonist. Despite this reservation, the chapter adequately covers the use of muscle relaxants in neurologic and muscular disease.

Malignant hyperthermia is covered in a separate section and provides a clear and comprehensive discussion of this disorder. Although the use of muscle relaxants in burn patients is covered in a separate chapter, this material easily could have been covered in the chapter on neuromuscular diseases.

This text will serve as a reference for anesthesiologists searching for advice concerning the handling of patients with respect to the use of neuromuscular blocking agents. A rather expensive volume, it would be of use to those having a particular interest in neuromuscular physiology and pharmacology. Though the individual anesthesiologist might not find it a worthwhile text, a group of anesthesiologists who are relatively busy and have a common departmental library would find that this book will provide many answers to their handling of a significant number of patients with respect to muscle relaxant use.

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Erratum

Addendum to 1987 Abstracts.

Page 378:

We wish to inform readers that the second line of the first sentence in this addendum should read: "Anesthesia Research Society 61st Congress . . .", rather than "60th".

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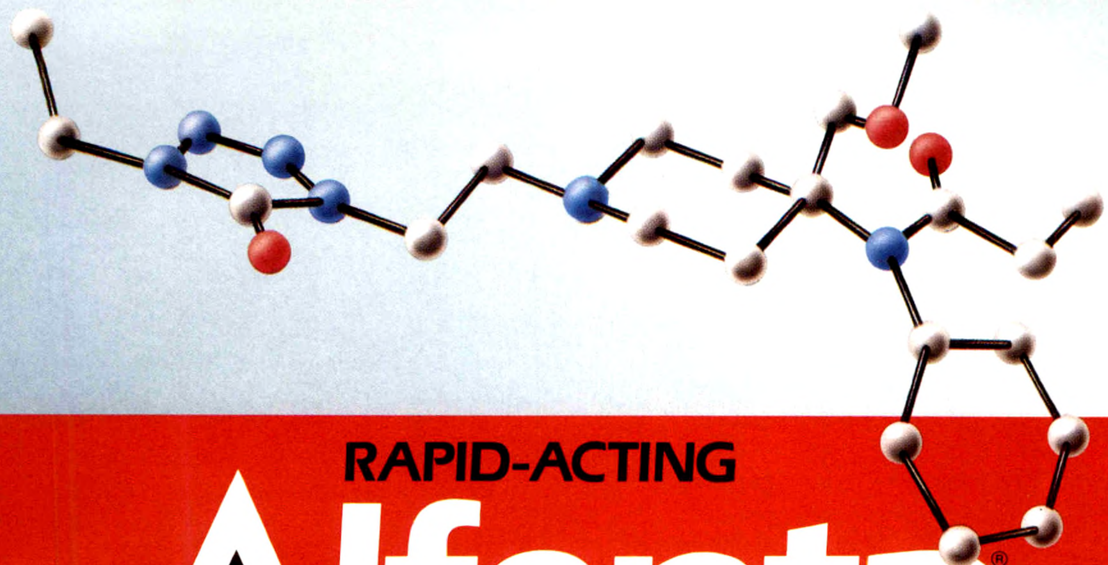

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ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 μg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 μg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to 1/4 of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 μg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 μg/kg).

The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.

General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight.

In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients.

In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged.

Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction.

Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery.

Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods.

The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent.

Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance.

Administration of ALFENTA infusion should be discontinued at leas 10-15 minutes prior to the end of surgery.

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.

Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction.

Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.

Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits.

There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.

Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 μg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.

Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.

ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported.

The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

	ALFENTA (N=785) %	Fentanyl (N=243) %	Thiopental Sodium (N=66) %	Enflurane (N=55) %	Halothane (N=18) %	Saline Placebo* (N=18) %
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were:

Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching.

Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.

DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD_{50} of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression.

The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

Manufactured by Taylor Pharmacal Co. for

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U.S. Patent No. 4,167,574
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See preceding page for brief summary of Prescribing Information for ALFENTA® (alfentanil HCl) Injection Ⓒ.

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